DESIGN AND DEVELOPMENT OF GLICLAZIDE MATRIX TABLETS USING HPC, HPMC AND THEIR COMBINATION AS A RELEASE RETARDING POLYMERS.

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THE TAMIL NADU Dr.M.G.R. MEDICAL UNIVERSITY

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In Partial fulfillment for the award of the degree of

MASTER OF PHARMACY

In

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Submitted by

Reg.No:261610274

Under the guidance of

Mr.V.KAMALAKKANNAN, M.Pharm.,

DEPARTMENT OF PHARMACEUTICS

J.K.K.NATTRAJA COLLEGE OF PHARMACY

KOMARAPALAYAM-638183, TAMILNADU.

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EVALUATION CERTIFICATE

This is to certify that the dissertation work entitled **"DESIGN AND DEVELOPMENT OF GLICLAZIDE MATRIX TABLETS USING HPC, HPMC AND THEIR COMBINATION AS A RELEASE RETARDING POLYMERS."** submitted by student bearing **Reg.No. 261610274** to **The TamilNadu Dr. M. G. R. Medical University,** Chennai, for the partial fulfillment of the degree of **MASTER OF PHARMACY** was evaluated by us during the examination held on……

Internal Examiner **External Examiner**

CERTIFICATE

This is to certify that the work embodied in the dissertation **"DESIGN AND DEVELOPMENT OF GLICLAZIDE MATRIX TABLETS USING HPC, HPMC AND THEIR COMBINATION AS A RELEASE RETARDING POLYMERS."** submitted to The TamilNadu Dr. M. G. R. Medical University, Chennai, was carried out by **Mr.NASEEF AHAMED.K.T Reg.No (261610274),** for the partial fulfillment of the degree of Master of Pharmacy in Pharmaceutics under direct supervision of **Mr.V.KAMALAKKANAN, M.Pharm., Asst.Professor**, Department of Pharmaceutics, J.K.K.Nattraja College of Pharmacy, Komarapalayam, during the academic year 2015-2016.

Place: Kumarapalayam.
Date:

Dr. R. Sambathkumar., M.Pharm., Ph. D.,
Principal,
J.K.K. Nattraja college of Pharmacy,
Kumarapalayam - 638183
TamilNadu

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Mr.V.Kamalakkannan., M.Pharm.,
Asst.Professor,
Department of Pharmaceutics,
J.K.K.Nattraja college of Pharmacy,
Kumarapalayam-638183.
Tamil Nadu.

Dr.R.Sambathkumar., M.Pharm., Ph.D.,
Principal,
J.K.K.Nattraja college of Pharmacy,
Kumarapalayam – 638183
TamilNadu

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Mr.V.Kamalakkannan., M.Pharm.,
Asst.Professor,
Department of Pharmaceutics,
J.K.K.Nattraja college of Pharmacy,
Kumarapalayam-638183.
Tamil Nadu.

Dr.R.Sambathkumar., M.Pharm., Ph.D.,
Principal,
J.K.K.Nattraja college of Pharmacy,
Kumarapalayam – 638183
TamilNadu

Dr.R.Sambathkumar, M.Pharm., Ph.D.,
Principal, Head of the Department,
J.K.K.Nattraja College of pharmacy,
Kumarapalayam-638183
Tamil Nadu

DECLARATION

The work presented in this dissertation entitled, **"DESIGN AND DEVELOPMENT OF GLICLAZIDE MATRIX TABLETS USING HPC, HPMC AND THEIR COMBINATION AS A RELEASE RETARDING POLYMERS"**was carried out by me, under the direct supervision of **Mr.V.KAMALAKKANNAN**, M.Pharm., Asst.Professor, Department of Pharmaceutics, J.K.K.Nattraja College of Pharmacy, Kumarapalayam.

I further declare that, the work is original and has not been submitted in part or full for the award of any other degree or diploma in any other university.

Place: Kumarapalayam. **Mr.NASEEF AHAMED**

Date : **Reg.No:**

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Mr.NASEEF AHAMED.K.T
Reg No: 261610274

ABSTRACT

In present investigation an attempt has been made to design and develop some Gliclazide matrix tablets using Hydroxy propyl cellulose, Hydroxy propyl methyl cellulose and their combination as release retarding polymers. Gliclazide is oral hypoglycaemic drug which lowers blood glucose level and has been selected to prepare sustained release dosage forms.

Gliclazide sustained release matrix tablets were prepared using Hydorxy Propyl Cellulose, Hydroxy Propyl Methyl Cellulose and their combination as base polymer by wet granulation method. FT-IR spectral analysis showed that characteristic peak of Gliclazide pure drug was retained in the spectra of all the formulations indicating the inactness of the drug in all the formulations. The prepared tablets were evaluated for number of parameters like thickness, diameter, weight variation, swelling index and *in vitro* release studies. All the prepared tablets were of smooth surface and elegant texture. The tablets prepared were checked visually for its appearance & surface texture. The weights of the tablets were in the range of 250 ± 5 mg. The thickness of the tablet was in the range of 4.45 ± 0.11 mm to 4.51 ± 0.12 mm

Gliclazide matrix tablets formulated employing HPMC K-4M and combination of HPMC K-4M and HPC 75-100 provided slow and controlled release of Gliclazide up to 12 hr.

Drug release from the matrix tablets formulation containing HPMC K-4M and HPC 75-100 follows first order drug release with non-fickian diffusion.

All the tablet formulation showed compliance with pharmacopoeial standard. As the time increases, the swelling index was increased; later on it decreases

Abstract

Gradually due to dissolution of outermost –gelled layer of tablet into dissolution medium. Comparison between HPMC K-4M, HPC 75-100 and their combination it has been observed that swelling index of HPMC K-4M was significantly more compared to HPC 75-100. Whereas swelling index in case of HPC 75-100 is less as compare to HPMC K-4M and HPC 75-100 combination. The dissolution result shows that an increased amount of polymer resulted in reduced drug release. A concentration dependent drug release is evident in case of the polymer i.e., lower concentration of polymers, release is marginally retarded at higher concentration is considerable.

Prepared matrix formulation containing HPMC K-4M (F_6), HPMC K-4M and HPC 75-100 combination (F_9) probably showing better release based up to 98 % to 99 % drug release within 12 hour.

Key words: sustained release, HPMC K-4M, HPC 75-100.

µg	:	micro gram
^0C	:	Degree centigrade
CDR	:	Cumulative Drug Released.
Conc.	:	Concentration.
$t_{50\%}$	:	Time of release of 50% of drug
$t_{90\%}$	:	Time of release of 90% of drug
F	:	Formulation
HPMC	:	Hydroxy Propyl MethylCellulose
HPC	:	Hydroxy Propyl Cellulose
GIT	:	Gastrointestinal tract
Hrs.	:	Hours
I.R	:	Infra red.
mm	:	millimeter
nm	:	Nanometer
RPM	:	Revolution per Minute
SR	:	Sustained Release
UV	:	Ultra violet
HPLC	:	High Performance Liquid Chromatography

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I. INDRODUCTION

Pharmaceutical products designed for oral delivery are mainly immediate release type or conventional drug delivery systems, which are designed for immediate release of drug for rapid absorption. These immediate release dosage forms have some limitations such as.

1) Drugs with short half-life requires frequent administration, which increases chances of missing dose of drug leading to poor patient compliance.
2) A typical peak-valley plasma concentration-time profile is obtained which makes attainment of steady state condition difficult.
3) The unavoidable fluctuations in the drug concentration may lead to under medication or overmedication as the C_{SS} values fall or rise beyond the Therapeutic range.
4) The fluctuating drug levels may lead to precipitation of adverse effects especially of a drug with small therapeutic index, whenever overmedication occurs. [1,2]of therapeutic benefits.

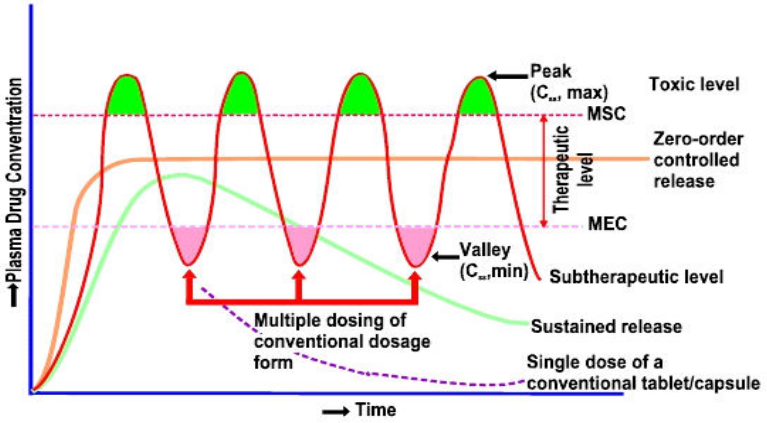

Fig. No: 1- A hypothetical plasma concentration-time profile from conventional multiple dosing and single doses of sustained and controlled delivery formulations.

In order to overcome the drawbacks of conventional drug delivery systems, several technical advancements have led to the development of controlled drug delivery system that could revolutionize method of medication and provide a number Of therapeutics benefits.

Sustained Release:

Sustained release tablet allowing a twofold or greater reduction in frequency of administration of a drug in comparison with the frequency required by a conventional dosage form. It is designed to maintain constant levels of a drug in the patient's bloodstream by releasing the drug over an extended period. Maintaining constant blood levels of the drug in the bloodstream increases the therapeutic effectiveness of the drug [3]

Advantages of sustained release formulations:-

1. Enhance patient compliance and convenience.
2. Reduction in dosing frequency.
3. Reduced fluctuations in circulating drug levels.
4. More uniform effect.
5. Employ less total drug that,
    a) Minimize or eliminates local side effects.
    b) Minimize or eliminates systemic side effects.
    c) Minimize drug accumulation with chronic dosing.
    d) Obtains less potentiation or reduction in drug activity on chronic use.
6. Safety margin of potent drug is increased by technically excellent designing of formulation.

7. Improve efficiency in treatment –by

   a) Cure or control of condition.

   b) Improve or control condition.

   c) Make use of specific effect.

   Eg.SR Aspirin for morning relief of arthritis

   d) Improve bioavailability of some drugs.

8. Patient care time is reduced.

9. Night time dosing can be avoided for patient convenience

10. Product life time is increased in sustained release formulations. Particles of drug are coated with matrix or entire product is matrix coated which along with its main function of sustained action, avoid exposure of unstable drug to the environment and render it stable. [4]

Disadvantages of sustained release formulations:

1. If there requires immediate change during the therapy or if any significant adverse effect is noted and prompt termination of therapy is needed, Sustained release does not permit immediate termination of therapy.
2. More costly process and equipment are needed in manufacturing of SRDF's.
3. Physician has less flexibility in adjusting dosage regimen as this is fixed by design of dosage form.
4. Risk of dose dumping, usually SRDF's contain drug amount that is 3-4 times more than conventional formulations. Sometimes this large quantity of drug may get rapidly released leading to toxicity.
5. Reduced drug absorption may delay onset of action. The effect of food on drug absorption kinetics may differ markedly from one SR formulations to another.

6. Drug absorbed at specific time in GIT cannot be formulated in SRDFs
7. Increased potential for first pass clearance.
8. For oral SRDF effective drug release is influenced and limited by GI Residence time.
9. SRDF's are designed for normal population that is on the basis of the biological half lives. Since disease state that alters drug dispositions as well as interpatient variability in pharmacokinetics parameters are not accommodated.
10. Drugs which are acted upon by enzymes in intestine undergo significant enzymatic breakdown as drug remains in body for longer time.
11. In case of accidental failure of the product effective antidote may be difficult to employ. [4]

1.2 Classification of sustained release drug delivery system:

Considering the mechanism of controlling the drug release the system is classified as follows:-

1. Chemically controlled systems
    a. Biodegradable system
    b. Drug polymer conjugates
2. Diffusion controlled systems
    a. Matrix diffusion
    b. Polymer erosion
    c. Polymer swelling
    d. Geometry [5]

A Useful Classification based on drug release from the SRDF is as follows:-

A. continuous release systems:-

These systems release the drug continuously for prolonged period of time along the entire length of GIT with normal transit time. [6]

Different systems under this class are –

1. Dissolution controlled release systems
2. Diffusion controlled release systems
3. Dissolution and diffusion controlled release systems
4. Ion exchange resin drug complex
5. Slow dissolving salts and complexes
6. pH dependent formulations
7. Osmotic pressure controlled systems
8. Hydrodynamic pressure controlled systems

B. Delayed transit and continuous release systems:-

These systems are designed to prolong release of drug with increased residence time in GIT. Such dosage forms are designed to remain in the stomach. Therefore the drug presented in such systems should be stable at gastric pH. This class includes following systems [7]

1. Altered density systems
2. Mucoadhesive systems
3. Size based systems

C. Delayed release systems:-

These systems are fabricated to release the drug only at specific site in the GIT. The drugs those are [7]

a. Destroyed in stomach or by intestinal enzymes
b. Known to cause gastric irritation
c. Absorbed from specific site in intestine, or exert local effect at specific GI site are formulated in such systems.

The two types of delayed release systems are:-

1. Intestinal release systems
2. Colonic release systems

Oral Controlled Drug Delivery Systems[7]:

Oral controlled release drug delivery is a drug delivery system that provides the continuous oral delivery of drugs at predictable and reproducible kinetics for a predetermined period throughout the course of GI transit and also the system that target the delivery of a drug to a specific region within the GI tract for either a local or systemic action.

All the pharmaceutical products formulated for systemic delivery via the oral route of administration, irrespective of the mode of delivery (immediate, sustained or controlled release) and the design of dosage form (either solid dispersion or liquid), must be developed within the intrinsic characteristics of GI physiology. Therefore the scientific framework required for the successful development of oral drug delivery systems consists of basic understanding of (i) physicochemical, pharmacokinetic and pharmacodynamic characteristics of the drug (ii) the anatomic and physiologic

characteristics of the gastrointestinal tract and (iii) physicochemical characteristics and the drug delivery mode of the dosage form to be designed.

The main areas of potential challenge in the development of oral controlled drug delivery systems are:-

1) Development of a drug delivery system: To develop a viable oral controlled release drug delivery system capable of delivering a drug at a therapeutically effective rate to a desirable site for duration required for optimal treatment.
2) Modulation of gastrointestinal transit time: To modulate the GI transit time so that the drug delivery system developed can be transported to a target site or to the vicinity of an absorption site and reside there for a prolonged period of time to maximize the delivery of a drug dose.
3) Minimization of hepatic first pass elimination: If the drug to be delivered is subjected to extensive hepatic first-pass elimination, preventive measures should be devised to either bypass or minimize the extent of hepatic metabolic effect.

Methods used to achieve controlled release of orally administered drugs.[8]

A. Diffusion Controlled System:

Basically diffusion process shows the movement of drug molecules from a region of a higher concentration to one of lower concentration. This system is of two types:

a) Reservoir type:

A core of drug surrounded by polymer membrane, which controls the release rate, characterizes reservoir devices.

***Advantages*:**

Zero order delivery is possible; release rate varies with polymer type.

***Disadvantages*:**

1) System must be physically removed from implant sites.
2) Difficult to deliver high molecular weight compounds.
3) Increased cost per dosage unit, potential toxicity if system fails.

Ficks first law of diffusion describes the diffusion process.

$J = - D \, dc/dx.$

D = diffusion coefficient in area/ time

dc/dx = change of concentration 'c' with distance 'x

b) Matrix type:

Matrix system is characterized by a homogenous dispersion of solid drug in a polymer mixture.

***Advantages*:**

Easier to produce than reservoir or encapsulated devices, can deliver high molecular weight compounds.

***Disadvantages*:**

Cannot provide zero order release, removal of remaining matrix is necessary for implanted system.

Higuchi has derived the appropriate equation for drug release from this system,

$M = K t^{1/2}$

M = amount of drug released per unit area,

K = Constant

B. Dissolution Controlled Systems:

a) Reservoir type:Drug is coated with a given thickness coating, which is slowly dissolved in the contents of gastrointestinal tract. By alternating layers of drug with the rate controlling coats as shown in figure no.2, a pulsed delivery can be achieved. If the outer layer is quickly releasing bolus dose of the drug, initial levels of the drug in the body can be quickly established with pulsed intervals.

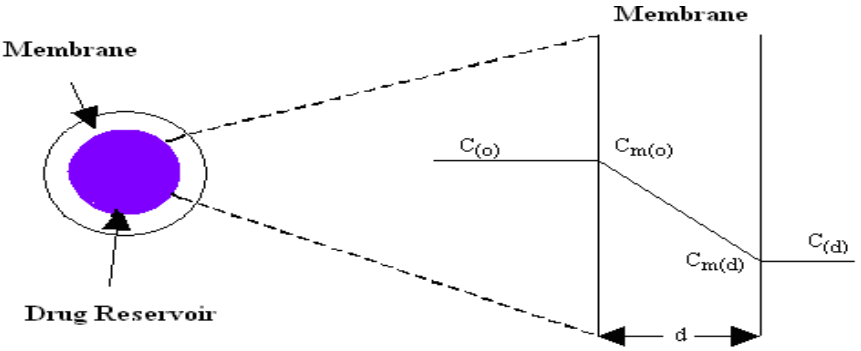

Fig.No.2: Schematic representation of diffusion controlled drug release reservoir system.

b) Matrix type:

The more common type of dissolution controlled dosage form as shown in figure no.3. It can be either a drug impregnated sphere or a drug impregnated tablet, which will be subjected to slow erosion.

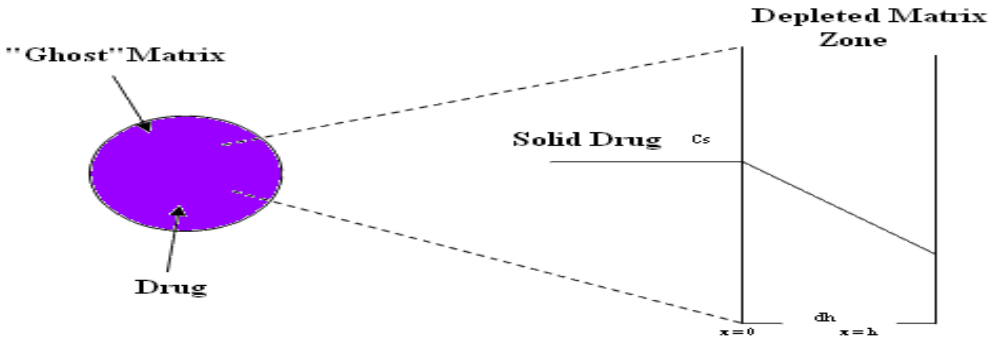

Fig.No.3: Schematic representation of diffusion controlled drug release matrix system.

C. Bioerodible and Combination of Diffusion and Dissolution Systems:

It is characterized by a homogeneous dispersion of drug in an erodible matrix.

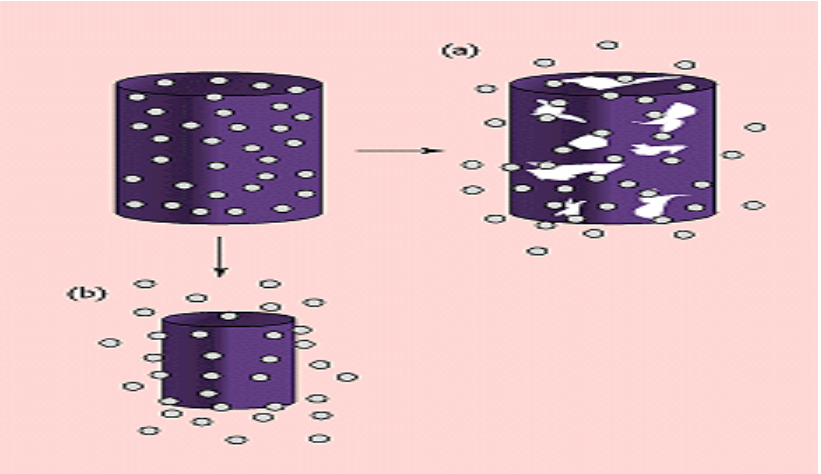

Fig.No.4: Drug delivery from (a) bulk-eroding and (b) surface-eroding Bioerodible systems.

Advantages:

- All the advantages of matrix dissolution system.
- Removal from implant site is not necessary.

***Disadvantages*:**

- Difficulty to control kinetics owing to multiple processes of release.
- Potential toxicity of degraded polymer must be considered.

D. Methods using Ion Exchange:

It is based on the drug resin complex formation when an ionic solution is kept in contact with ionic resins. The drug from these complexes gets exchanged in gastrointestinal tract and released with excess of Na^+ and Cl^- present in gastrointestinal tract.

E. Methods using osmotic pressure:

It is characterized by drug surrounded by semi permeable membrane and release governed by osmotic pressure.

Advantages:

Zero order release rates are obtainable.

Preformulation is not required for different drugs.

Release of drug is independent of the environment of the system.

Disadvantages:

System can be much more expensive than conventional counterparts.

Quality control is more extensive than most conventional tablets.

F. pH– Independent formulations:

A buffered controlled release formulation is prepared by mixing a basic or acidic drug with one or more buffering agents, granulating with appropriate pharmaceutical excipients and coating with GI fluid permeable film forming polymer. When GI fluid permeates through the membrane the buffering agent adjusts the fluid inside to suitable constant pH thereby rendering a constant rate of drug release.

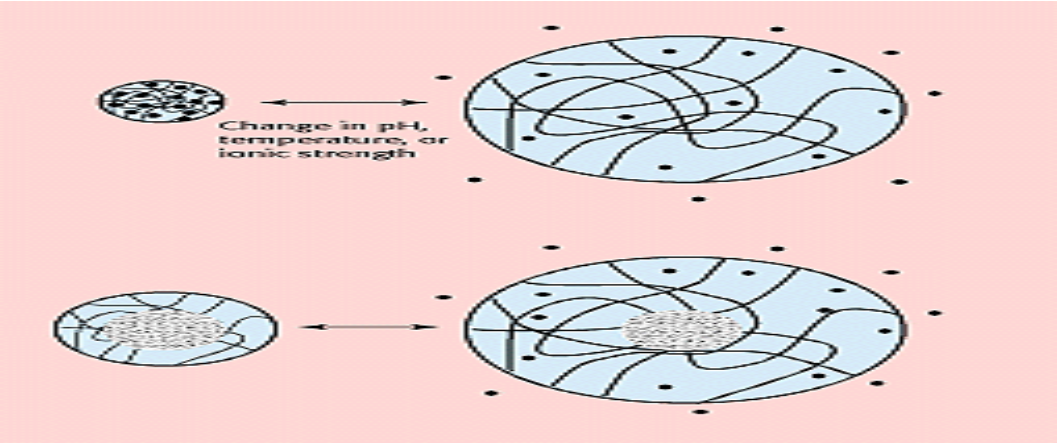

Fig.No.5: Drug delivery from environmentally pH sensitive release systems.

G. Altered density formulations:

Several approaches have been developed to prolong the residence time of drug delivery system in the gastrointestinal tract.

High-density approach

Low-density approach

Fabrication of oral controlled release delivery employs various methods:[9]

Hydrophilic matrix, Plastic matrix, Barrier resin beads, Fat embedment, Repeat action, Ion exchange resin, Soft gelatin depot capsules and Drug complex.

Hydrophilic Matrix System:

Drug delivery technologists usually tend to consider all hydrophilic delivery systems as hydrogels. Hydrogels are hydrophilic macromolecular networks that after swelling maintain their shape due to permanent links. The very high water content and special surface properties of swollen form give them the ability to simulate natural tissues[10].

They have been used in controlled drug delivery because of their good tissue compatibility and easy manipulation of swelling level and there by solute permeability[11].

The most widely used polymers for drug delivery control; particularly in oral applications are swellable polymers.

Hydrogel based Drug Delivery Systems are classified as:

Diffusion Controlled Release System

a) Reservoir System: It consists of polymeric membrane surrounding a core containing the drug. The rate-limiting step for drug release is diffusion through the outer membrane of the device.

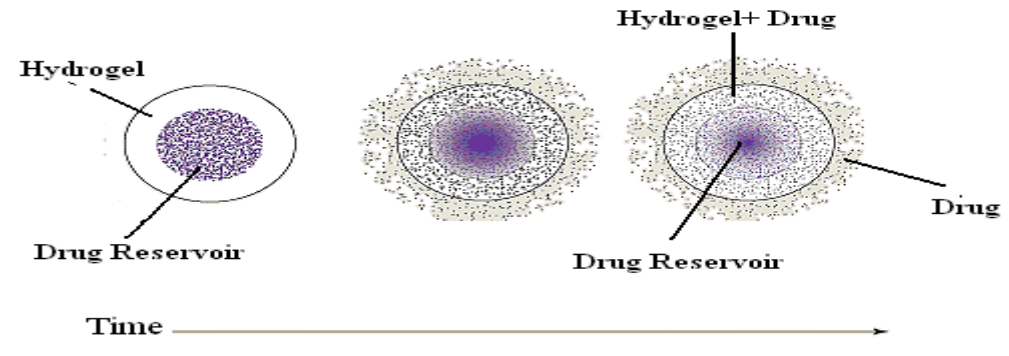

Fig. No.6: Hydrogel formation in Reservoir Systems.

b) Matrix System:

The drug is dispersed through out the three dimensional structure of the hydrogel. Release occurs due to diffusion of the drug throughout the water filled pores.

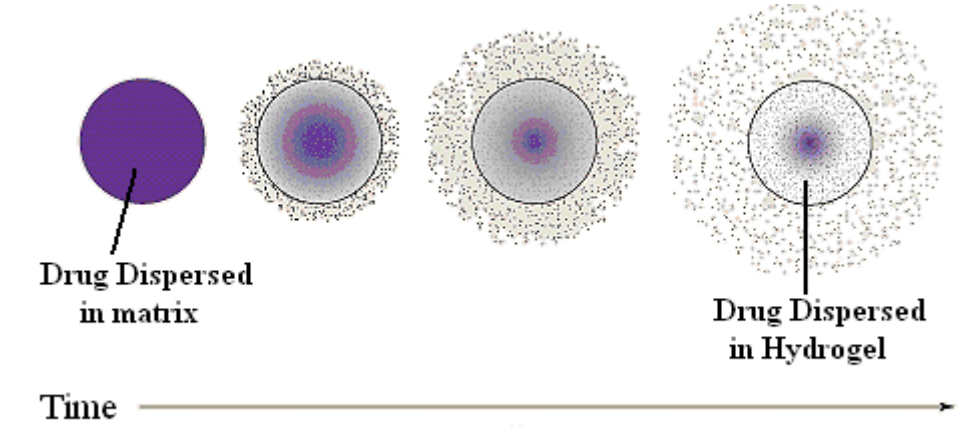

Fig. No.7: Hydro gel formation in Matrix System.

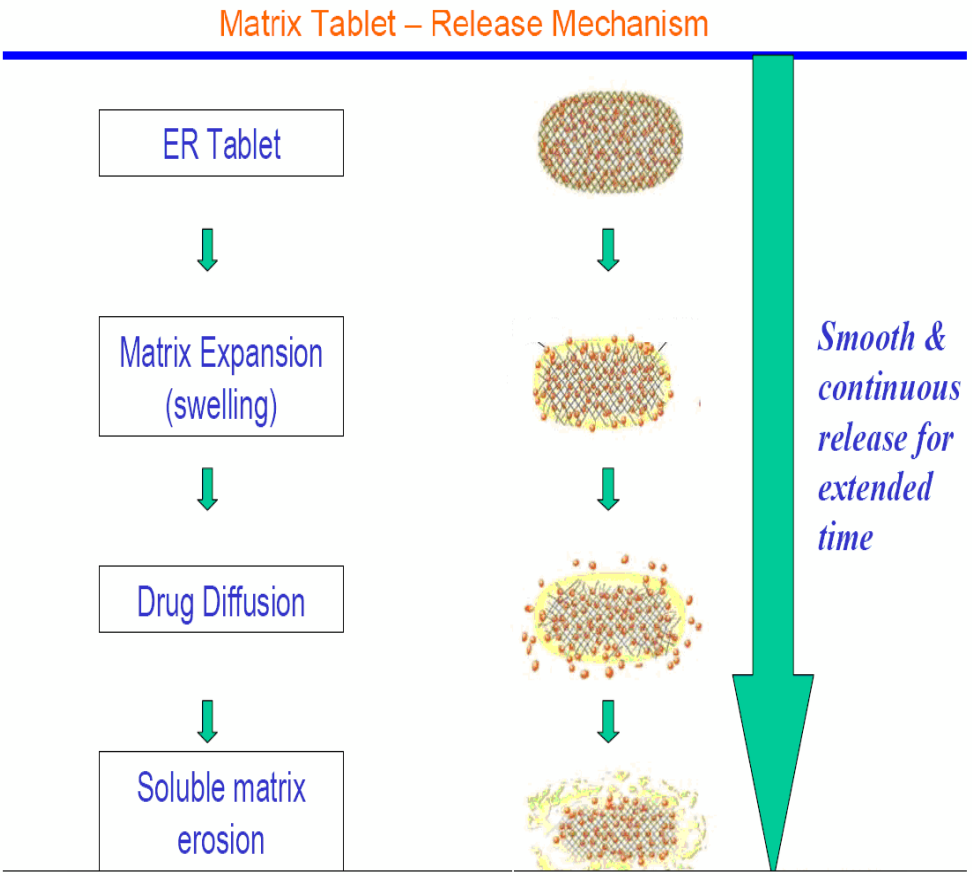

Fig. No.8: Drug release from a matrix tablet

Types:

- Swellable.
- Non-swellable.

Swellable Controlled Release Systems:

During the release life of swellable matrix system, three fronts are generally expected.

1. The swelling front, the boundary between the still glassy polymer and its rubbery state.
2. The diffusion front, the boundary in the gel layer between the solid as yet undissolved, drug and the dissolved drug.
3. The erosion front, the boundary between the matrix and the dissolution medium.

The measurement of front positions gives the possibility to determine three important parameters related to the behavior of the matrix i.e. the rate of water uptake, the rate of drug dissolution and the rate of matrix erosion associated with the movements of the swelling front, diffusion front and erosion front respectively.

These parameters are strictly linked to the drug release kinetics from matrix.

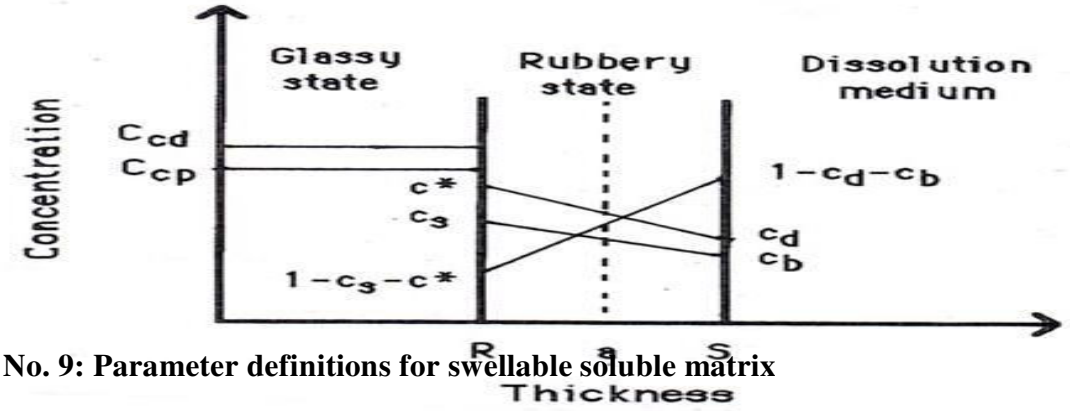

Fig. No. 9: Parameter definitions for swellable soluble matrix

Ds – Solvent diffusion co-efficient in the drug/ polymer matrix.

Dd – Drug diffusion co-efficient in the swollen polymers.

Cs – Drug solubility at the drug core interface (R)

C* - Drug volume fraction at the gel/solution interface

C – Polymer volume fraction at R

Cd – Polymer volume fraction at S.

Ccp- Polymer volume fractioning in the glassy core

Ccd - Drug volume fraction in the glassy core.

Non-swell able controlled release systems:

These systems are hollow containing an inner core of drug surrounded in a water insoluble polymer membrane. The polymer can be applied by coating or by wet granulation technique. The drug release mechanism across the membrane involves its partitioning into the membrane with subsequent release into the surrounding fluid by diffusion.

The polymers commonly used in such devices are Hydroxy Propyl Cellulose, Ethyl Cellulose and Polyvinyl Acetate. A disadvantage of all such release system is a chance of sudden drug dumping which is not common with matrix devices.

AIM &OBJECTIVES

- The basic goal of therapy is to achieve a steady state blood or tissue level that is therapeutically effective and non-toxic for an extended period of time. Sustained release drug delivery systems, with an aim of improved patient compliance, better therapeutic efficacy, less side effects and reduced dosage regimen with less toxicity for treatment for many acute and chronic diseases**.**
- Gliclazide is oral hypoglycaemic drug which lowers blood glucose level. It provokes a brisk release of insulin from pancreas and shows peculiar pharmacokinetic characteristics. It is extensively protein bound (87% to 94%) in circulation. It is first sulfonylurea for which it is possible to detail its action from the moment of oral administration through to it's on long term glycemic control. Its plasma peak concentration occurs between 4 to 6 hours. Therefore, gastric and intestinal transient times have a significant effect on the rate and extent of oral absorption of the drug.
- Matrix tablets are very useful in the field of healthcare for sustained release dosage regimen.
- Keeping this in view, the present investigation has been aimed at designing suitable sustained release matrix tablets using polymers as hydroxylpropyl methylcellulose and hydroxyl propyl cellulose.

The major objectives of the investigation are as follows:

1. To perform preformulation studies like flowing properties & bulking density for powders of drug and polymers.

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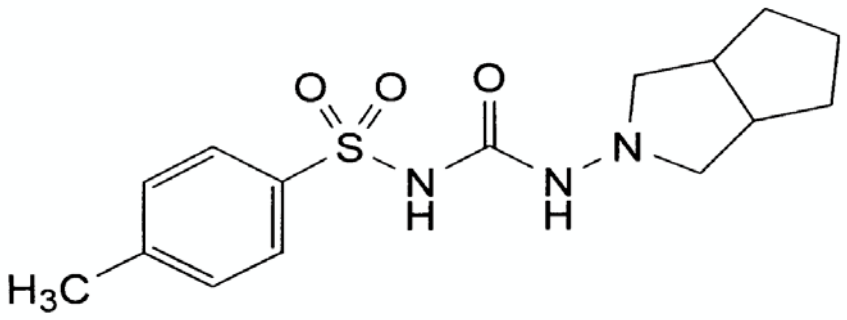
2. To formulate matrix tablets of Gliclazide by wet granulation method by using different polymers like HPMC, HPC
3. To evaluate prepared formulations for physical parameters like weight variation, friability, and hardness etc.
4. To study swelling index behavior of selected formulation.
5. To study *in-vitro* drug release performance of different tablets formulations.
6. To study the effect of different polymers on drug release.
7. To ascertain the release mechanics and kinetics of drug release from compressed matrix tablets.
8. To perform stability studies as per ICH guidelines.

BASIS FOR DRUG SELECTION AND DOSAGE SELECTION.

- For many drugs, the optimal therapeutic response is observed only when adequate blood levels are achieved and maintained with minimum variations, (the matrix tablets will give more consistent blood levels).
- Sulfonylurea with long half-life such as gliclazide has sustained stimulation on insulin secretion compared to repaglinide which has short half-life for only about 1 hr.
- Gliclazide with biological half-life is 10 to 12hrs. It is oral hypoglycaemic drug which lowers blood glucose level and extensively protein bound in circulation.
- It has been recommended for use on the basis of both its metabolic and non metabolic effects.

DRUG & EXCIPIENTS PROFILE

GLICLAZIDE.[12, 13, 14, 15]



$C_{15}H_{21}N_3O_3S$, Mol. Wt: 323.4

Gliclazide, 1-(3-azabicyclo (3.3.0) oct-3-yl)-3-*p*tolylsulphonylurea is an oral hypoglycemic agent used in the treatment of non-insulin-dependent diabetes mellitus (NIDDM). It contains not less than 99.0 % and not more than the equivalent of 101.0% of 1-(hexahydrocyclopenta[*c*]pyrrol-2(1*H*)-yl)-3-[(4-methylphenyl)sulphonyl]urea, calculated with reference to the dried substance.

Characteristics:

A white or almost white powder.

Solubility:

Practically insoluble in water, freely soluble in methylene chloride, sparingly soluble in acetone, slightly soluble in alcohol.

Pharmacological effects:

Gliclazide is oral hypoglycaemic drug which lowers blood glucose level. It provokes a brisk release of insulin from pancreas and shows peculiar pharmacokinetic characteristics.

Pharmacokinetics:

It is extensively protein bound (87% to 94%) in circulation. It is first sulfonylurea for which it is possible to detail its action from the moment of oral administration through to it's on long term glycemic control. Its plasma peak concentration occurs between 4 to 6 hours. Therefore, gastric and intestinal transient times have a significant effect on the rate and extent of oral absorption of the drug.

Therapeutic uses:

This medication is used in conjunction with diet and exercise regimens to control high blood sugar in non-insulin dependent diabetic patients. Controlling high blood sugar helps prevent heart disease, strokes, kidney disease, circulation problems, and blindness.

Preparation:

Gliclazide tablets each containing 30 mg, 40 mg and 60 mg of Gliclazide are official in USP and BP. Tablets containing 30 mg and 40 mg of Gliclazide are available commercially in the market.

Mechanism of action:

Sulfonylureas provoke a brisk release of insulin from pancreas. They act on the so called sulfonylurea receptors (SUR1) on the pancreatic β cell membrane-cause depolarization by reducing conductance of ATP sensitive K^+ channels. This enhances Ca^{2+} influx degranulation. The rate of insulin secretion at any glucose concentration is increased. In type 2 DM the kinetics of insulin release in response to glucose or meals is delayed and subdued.

Dose:

Adult dose: - 40 mg to 240 mg twice a day.

Side effects:

Hypoglycaemia: - It is the commonest problem, may occasionally be severe and rarely fatal. It is more commonly in elderly, liver and kidney disease patients and when potentiating drugs are added.

Hypersensitivity: - Rashes, photosensitivity, purpurea, transient lukopenia, rarely agranulocytosis.

Nonspecific side effects: - Nausea, vomiting, flatulence, diarrhea or constipation, headache, paresthesias and weight gain

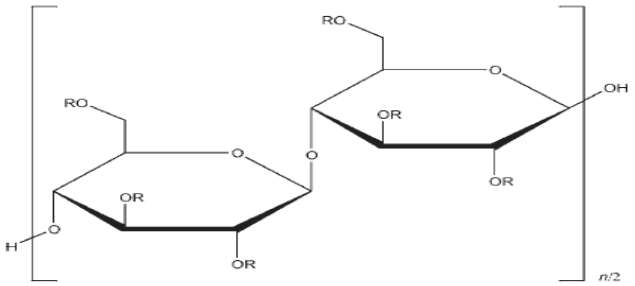
POLYMER PROFILE [16]:

HYDROXYPROPYL METHYLCELLULOSE

Chemical name **:** Cellulose hydroxypropyl methyl ether

Molecular weight **:** 10 000–1 500 000

Chemical Structure:



The substituent R represent either a-CH_3, or a $–CH_2CH(CH_3)OH$ group, or a hydrogen atom.

Description:

Hypromellose is an odorless and tasteless, white or creamy-white fibrous or granular powder.

Melting point: Browns at 190–200^{0}C; chars at 225–230^{0}C. Glass transition temperature is 170–180^{0}C.

Viscosity (dynamic): A wide range of viscosity types are commercially available. Aqueous solutions are most commonly prepared, although hypromellose may also be dissolved in aqueous alcohols such as ethanol and propan-2-ol provided the alcohol content is less than 50% w/w

Incompatibility: - Hypromellose is incompatible with some oxidizing agents. Since it is nonionic, hypromellose will not complex with metallic salts or ionicorganics to form insoluble precipitates.

Stability and Storage:

Hypromellose powder is a stable material, although it is hygroscopic after drying. Solutions are stable at pH 3–11. Hypromellose undergoes a reversible sol–gel transformation upon heating and cooling, respectively. The gelation temperature is 50–98^{0}C, depending upon the grade and concentration of material. For temperatures below the gelation temperature, viscosity of the solution decreases as temperature is increased. Beyond the gelation temperature, viscosity increases as temperature is increased. Hypromellose powder should be stored in a well-closed container, in a cool, and dry place.

Applications in pharmaceutical formulation or technology:

Accepted for use as a food additive in Europe. Included in the FDA Inactive Ingredients Database (ophthalmic and nasal preparations; oral capsules, suspensions, syrups, and tablets; topical and vaginal preparations). Hypromellose has been used in pharmaceutical dosage forms produced using hot-melt extrusion. Hypromellose is also used as a suspending and thickening agent in topical formulations. Hypromellose

is used as an emulsifier, suspending agent, and stabilizing agent in topical gels and ointments.

HYDROXYPROPYL CELLULOSE

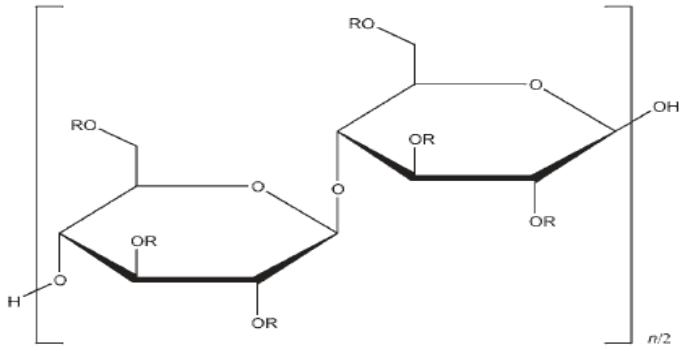
Synonyms: Cellulose, hydroxypropyl ether; E463; hydroxypropylcellulosum; hyprolose; Klucel; Nisso HPC; oxypropylated cellulose.

Chemical name:

Cellulose, 2-hydroxypropyl ether

Molecular Weight: 50000–1250000

Structural Formula:



R is H or [CH_2CH (CH_3) O] mH where m is a common integral number of cellulose derivatives.

Description: - Hydroxypropyl cellulose is a white to slightly yellow-colored, odorless and tasteless powder

Melting point: - Softens at 130^0C; chars at 260–275^0C

Incompatibilities: - Hydroxypropyl cellulose in solution demonstrates some incompatibility with substituted phenol derivatives, such as methylparaben and propylparaben. The presence of anionic polymers may increase the viscosity of hydroxypropyl cellulose solutions

Stability and storage condition: - Hydroxypropyl cellulose powder is a stable material, although it is hygroscopic after drying. Hydroxypropyl cellulose powder should be stored in a well closed container in a cool and dry place.

Pharmaceutical Uses:

Hydroxypropyl cellulose is widely used in oral and topical pharmaceutical formulations. In oral products, hydroxypropyl cellulose is primarily used in tableting as a binder, film-coating, and extended-release-matrix former. Concentrations of hydroxypropyl cellulose of 2–6% w/w may be used as a binder in either wet-granulation or dry, direct compression tableting processes. Concentrations of 15–35% w/w of hydroxypropyl cellulose may be used to produce tablets with an extended drug release. The release rate of a drug increases with decreasing viscosity of hydroxypropyl cellulose. It is also used in microencapsulation processes and as a thickening agent. Hydroxypropyl cellulose is also used in cosmetics and in food products as an emulsifier and stabilizer.

Safety: Excessive consumption of hydroxypropyl cellulose may have a laxative effect.

DICALCIUM PHOSPHATE

Non-Proprietary name:

Calcium diphosphate. C-131<.

Synonym:

(DCP) dicalcium phosphate, calcium dihydrophosphate.

Incompatibilities:

With some drugs which form a complex (complexation reaction) and retain in kidneys as oxalate complexes.

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Chemical name:

[$CaHPO_4 2H_2O$]

Molecular weight:

172.10.

Category:

Tablet and capsule diluents and filler.

Description:

White to off-white powder. DCP is odorless and tasteless inert powder.

Solubility:

Insoluble in water and other organic fluids.

Stability:

Stable under humid conditions and no bacterial or mould growth occur, which is stable for prolonged storage. It is resistible to warm and damp conditions.

Storage:

To be stored in a well closed container, cool and dry place.

Safety:

Adverse reactions to DCP are very leastly attributed to intolerance, but may have chance of accumulation in kidneys as cyst and stones which may be complicative in rare cases.

Particle size:

(230 mesh #) – 98% passes.

Minimum assay:

98 – 102.5%

Loss on drying:

24.5 – 26.5%

Loss on ignition:

800ºC up to 80%.

Substance insoluble in HCl:

0.1%.

POLYVINYL PYRROLIDINE

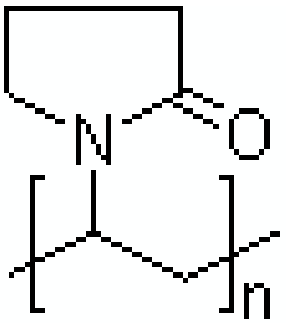
Synonym:

Plasdone K-30, Luviskol K30, Plasdone, Povidone, PVP P, PVP-K 30; PVP; Polyvinylpyrrolidone; Poly [1-(2-oxo-1-pyrrolidinyl) ethylene); Povidone K-30; Poly(n-vinlybutyrolactam);Poly(1-vinylpyrrolidinone);

Chemical Name: Poly (1-vinyl-2-pyrrolidinone)

Chemical Formula: (C6H9NO)n

Chemical structure:



Physical state and appearance: Solid. (Powdered solid.)

Odor: Odorless.

Molecular Weight: (111.14) n g/mole

Color: Creamy White.

Boiling Point: 90°C (194°F) - 93 C

Melting Point: 13.9°C (57°F)

Specific Gravity: Density: 1.23 - 1.29(Water = 1)

Incompatibility with various substances: Reactive with oxidizing agents

Solubility:

- Soluble in cold water.
- Soluble in water giving a colloidal solution.
- Soluble in chloroform, alcohol, chlorinated hydrocarbons, amines, nitro paraffin's, lower weight fatty acids.

Specification:

1. Application:

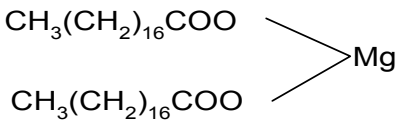
   PVP K series can be used as film forming agent, viscosity-enhancement agent, lubricator and adhesive. They are the key component of hair sprays, mousse, gels and lotions & solution. They are also convenience assistant in skin care product, hair-drying reagent, shampoo, eye makeup, lipstick, deodorant, sunscreen and dentifrice.

2. Pharmaceutical:

Povidone K 30 and K 25 is a new and excellent pharmaceutical excipient. It is mainly used as binder for tablet, dissolving assistant for injection, flow assistant for capsule, dispersant for liquid medicine and pigment, stabilizer for enzyme and heat sensitive drug, co precipitant for poorly soluble drugs, lubricator and antitoxic assistant of eye drug. PVP has been used as excipients in more than one hundred drugs.

Molecular Weight: 591.3

Structure:



Description:

Fine, white, precipitated or milled, impalpable powder of low bulk density. Odor and taste are slight but characteristic. The powder readily adheres to the skin.

Typical Properties:

Solubility:

Insoluble in water, alcohol and ether. Slightly soluble in hot alcohol and benzene.

Stability and storage conditions:

Stable, non-self-polymerizable. Store in a cool, dry place in a well closed container.

Incompatibilities:

Acidic substances; alkaline substances; iron salts. Avoid mixing with strong oxidizing materials. Use with caution with drugs, which are incompatible with alkali.

Safety:

It is described as an inert or nuisance dust. Classified as non-hazardous by the Department of Transportation Regulations. Dust clouds of magnesium stearate may be explosive.

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COLLOIDAL SILICON DIOXIDE

Synonyms: Aerosil; Cab-O-Sil; Cab-O-Sil M-5P; colloidal silica

Chemical name: Silica

Empirical formula: SiO_2

Molecular Weight: 60.08

Structure:

Description: It is a light, loose, bluish-white-colored, odorless, tasteless, amorphous powder

Melting point: 1600^0C

Solubility: Practically insoluble in organic solvents, water, and acids, except hydrofluoric acid; soluble in hot solutions of alkali hydroxide.

Incompatibilites: Incompatible with diethylstilbestrol preparations.

Stabilities and Storage condition: Colloidal silicon dioxide is hygroscopic but adsorbs large quantities of water without liquefying. When used in aqueous systems at a pH 0–7.5, colloidal silicon dioxide is effective in increasing the viscosity of a system. Colloidal silicon dioxide powder should be stored in a well-closed container

Application: Colloidal silicon dioxide is widely used in pharmaceuticals, cosmetics, and food products. Colloidal silicon dioxide is also used to stabilize emulsions and as a thixotropic thickening and suspending agent in gels and semisolid preparations. In aerosols, other than those for inhalation, colloidal silicon dioxide is used to promote particulate suspension, eliminate hard settling, and minimize the clogging of spray nozzles. Colloidal silicon dioxide is also used as a tablet disintegrant and as an adsorbent dispersing agent for liquids in powders.

AN EXTENSIVE WORK WAS CARRIED ON MATRIX, SOME OF THEM ARE CITED BELOW.

1. Jeyaprabha P et al The purpose of this research work was to prepare a modified release tablet of gliclazide by using different grades of Hydroxypropyl cellulose. Infrared spectroscopy study showed that drug and other excipients were compatible with each other. The granules were evaluated for angle of repose, bulk density and compressibility index. The tablets were evaluated to weight variation, thickness, hardness, friability, drug content, *in-vitro* drug release. The granules showed satisfactory flow properties. This study showed that release process involved erosion and diffusion. The Accelerated stability study was also performed for optimized formulation for three months indicated that optimized formulation was stable.[17]

2. Hindustan AA et al The formulation was to design matrix type oral tablets of Gliclazide with *Azadirachta indica* fruit mucilage and Povidone. The polymers were studied for its functionality as a matrix forming property to sustain the Gliclazide release from formulated matrix tablets. Physicochemical properties of dried powdered mucilage of *Azadirachta indica* fruit mucilage and Povidone blend were studied. Various formulations of Gliclazide *Azadirachta indica* fruit mucilage and Povidone were prepared. The swelling behavior and release rate characteristics were studied. The *in-vitro* dissolution study proved that the dried *Azadirachta indica* fruit mucilage.[18]

3. Sapkal NP et al Gliclazide has been found to form inclusion complexes with β-cyclodextrin (β-CD) in solution and in solid state. The present study was undertaken to determine a suitable method for scaling up gliclazide-β-CD inclusion complex formation and to evaluate the effect of some parameters on the efficiency of complexation.

The solid inclusion complexes of gliclazide and β-cyclodextrin were prepared at a molar ratio of 1:1 and 1:2 by mixing, kneading, and coprecipitation methods both on small and large scales.Characterization was performed using infrared spectroscopy, X-ray diffractometry, and dissolution studies. In vitro release studies were carried out in phosphate buffer (pH 6.8).[19]

4. Prameela RA et al The antidiabetic drugs are poorly soluble in water, which affect the bioavailability. In the present work, complex formation of all the three drugs with β- cyclodextrin (β-CD) and Hydroxy propyl b- cyclodextrin (HPβ-CD) and then the possibility of improving the solubility of NTG, RPG and GMP by complexation with β-CD, HPβ-CD were investigated. The phase solubility studies indicated the formation of Nateglinide-β-CD, Repaglinide-β-CD, Glimepiride-β-CD, Nateglinide- HPβ-CD, Repaglinide-HPβ-CD and Glimepiride-HPβ-CD inclusion complexes at 1:1 M ratio in solutions with stability constant of 345 M-1, 267 M-1,329 M-1, 433 M-1,319 M-1, and 406 M-1 respectively. The solubility was markedly enhanced by complexation with β-CD and HPβ-CD.[20]

5. Moyano JR et al Solid complexes between gliclazide and fl-cyclodextrin (fl-CD) were prepared by kneading, coprecipitation, neutralization, co-rindingandspray-drying.Characterization of gliclazide-fl-CD inclusion complexes was performed using X-ray diffractometry and cross polarizing/magic angle spinning ~3C-nuclear magnetic resonance spectroscopy. The complexes, obtained by neutralization and spray-drying methods, showed enhanced dissolution rates of gliclazide.[21]

6. Biswal S, Sahoo J et al Gliclazide SDs containing varying concentrations of PEG 8000 were prepared using the fusion – solvent technique, and their phase solubility behavior and dissolution in 0.1N HCl were assessed at 37^0C. The physical state of, and gliclazide- PEG interactions in, SDs and physical mixtures prepared in ratios of 1:1, 1:2 and 1:5 (gliclazide: PEG 8000), respectively, were characterized by x-ray diffraction (XRD), Fourier-transform infrared (FTIR) spectroscopy and differential scanning Calorimetry (DSC).[22]

7. Vijayalakshmi P et al The antidiabetic drug gliclazide has very poor aqueous solubility leading to variable bioavailabilities on oral administration thus posing problems in the design of controlled release tablets. Therefore, the aim of the study was to increase the solubility of the drug by making inclusion Complex with hydroxypropylbetacyclodextrin in the ratio 1:2 and to incorporate the solubility enhanced drug in matrix forming polymer like sodiumcarboxymethylcellulose for designing oral controlled release tablets.[23]

8 Esra D, Levent O et al Gliclazide is a second generation sulfonylurea drug, characterized by poor solubility and, hence, by a low dissolution rate in water. This property causes inter- individual variations of its bioavailability. The major drawback in the therapeutic application and efficacy of gliclazide as oral dosage forms is its very low aqueous solubility because of its hydrophobic nature.[24]

9. The present invention relates to a sugar-free sustained-release gliclazide formulation omprising an intragranular part and an extragranular part, wherein the intragranular part comprises gliclazide or a salt thereof and the extragranular part comprises a cellulose-derived polymer, said intragranular part being binder-free.

The sustained-release formulation of the inventionpreferably consists essentially of gliclazide or a salt there of a diluent - an extragranular cellulose-derived polymer, a lubricant and/or glidant.[25]

10. Raida SA et al This work investigates preparation of biodegradable beads with alginate polymer by ionotropic gelation method to take the advantages of the swelling and mucoadhesive properties of alginate beads for improving the oral delivery of the antidiabetic agent gliclazide. It demonstrates that the ionic gelation of alginate molecules offers a flexible and easily controllable process for manipulating the characteristics of the beads which are important in controlling the release rate and consequently the absorption of gliclazide from the gastrointestinal tract. Variations in polymer concentration, stirring speed, internal phase volume and the type of surfactant in the external phase were examined systemically for their effects on the particle size, incorporation efficiency and flow properties of the beads. The *in vitro* release experiments revealed that the swelling is the main parameter controlling the release rate of gliclazide from the beads.[26]

11. Ambrogi V et al This paper deals with a new hydrotalcite-like compound used as a matrix to improve dissolution rate of the poorly water-soluble drug gliclazide and to administer at the same time micro- and oligo-elements useful to improve insulin performance. Gliclazide is a second-generation sulfonylurea compound used in the treatment of type II diabetes mellitus. As a consequence of the poor water solubility, its absorption is limited. Thus, a new hydrotalcite-like compound containing Zinc and Chromium, micronutrients directly involved in the physiology of insulin and in the carbohydrate, lipid and protein metabolism, was synthesized. The gliclazide-hydrotalcite-like clay

nanohybrid was prepared via ion-exchange in its nitrate form and was characterized by inductively coupled plasma-optical emission spectrometry and thermogravimetric analysis. The intercalation product was submitted to solubility measurements and in vitro dissolution test.[27]

12. Guntram S et al Gliclazide modified release (MR) is a new formulation of the drug gliclazide and is given once daily. The specifically designed hydrophilic matrix of gliclazide MR leads to a progressive drug release that parallels the 24-hour glycemic profile in type 2 diabetic patients. Development studies showed a sustained efficacy over 2 years coupled with a very good acceptability. Gliclazide MR acts selectively on adenosine triphosphate–dependent potassium (K_{ATP}) channels of the pancreatic β cell. No interaction with cardiovascular K_{ATP} channels has been shown, indicating that the drug can be safely used in patients with ischemic heart disease.[28]

13. Saify ZS et al The goal of rational drug therapy is to produce a desired pharmacological response in an acceptable and predictable manner while minimizing the occurrence of undesired events. The Pharmacokinetics of different generics of tablet gliclazide 80 mg was investigated on healthy (10 x 2), Pakistani subjects. For this exploration an open-label, randomized, two period crossover (Balanced in Complete Block Design) study, was conducted The outcome of the said study suggests that all generics were found analogous regarding pharmacokinetic behavior in-spite of having different excipients, concentration of excipients, sources of raw material, manufacturing process, machinery, resources and also inter individual variation of the study. Results of the study also undoubtedly advocate that generics manufactured in different manufacturing units of Pakistan are near to the standard formulation and produce comparable results. No significant

differences in pharmacokinetics parameters were observed, however, minor differences might narrate with inter individual variation in human volunteers and in different generic as well as different pharmaceutical unit.[29]

14. Hong SS et al A soft gelatin capsule containing PEG 400, PEG 4000, Tween 20 and glycerin was prepared as a formulation that may accelerate dissolution of gliclazide. The in vitro dissolution of gliclazide at pH 7.2 was identical for the soft capsule and conventional tablets, Diamicron and Diberin. However, at pH 1.2 and 4.0, the dissolution from the soft capsule was more rapid compared to the tablets. When bioavailability parameters were compared following oral administration of the soft capsule and Diamicron to 16 healthy Korean male subjects, the parameters representing the amount of absorption (i.e. the area under the serum gliclazide concentration vs. time curve up to 24 h, AUC, and the peak serum concentration, C) were not statistically different for both formulations. However, the time 24 max required to reach the peak (T) was significantly shorter for the soft capsule than for the Diamicron. Our results, therefore, max indicate that a rapid elevation of serum gliclazide concentration following oral administration of a formulation can be achieved by accelerating the in vitro dissolution of gliclazide from the formulation into the acidic buffers.[30]

15 Varshosaz J et al Gliclazide (GL) is a second-generation sulphonylurea, widely used for the treatment of non-insulin dependent diabetes mellitus. The low water-solubility of GL leads to a low dissolution rate and variable bioavailability. The aim of this study was to enhance the dissolution rate of GL by the preparation of micron-sized particles using a solvent change method.

stabilizing agents. GL (0.5 or 1 g) was dissolved in acetone and the stabilizing agent in water (as non-solvent). The non-solvent was poured rapidly into the drug solution under stirring at 26,000 rpm by an ultra-homogenizer, and the resultant was freeze-dried. The crystalline shape of GL changed from rod-shape to diamond- or cube-shape. The FTIR and DSC results showed no interaction between the drug and the stabilizers. Presence of sharp peaks in the XRD diffract grams of micro crystals with 10 times smaller height than untreated crystals indicates that a crystalline habit modification has occurred in the microcrystal without any polymorphic changes..[31]

16. Ozkan Y et al Inclusion complexes of gliclazide with β-cyclodextrin were prepared using different two methods: neutralization and recyristalization. Host–guest interactions were studied in the solid state by X-ray diffractometry and infrared spectroscopy. The stability constant between gliclazide and β-cyclodextrin was calculated from the phase solubility diagram. It was found that the neutralization technique and a solid complex of gliclazide with β-cyclodextrin in a molar ratio of 1.5:1 could be used to prepare the amorphous state of drug inclusion complexes. The dissolution rate of gliclazide from the inclusion complex made by neutralization was much faster than the pure drug, physical mixture of drug and cyclodextrin, recyristalization system and also comparable to the data reported in literature. [32]

17. Revathi R et al A simple, sensitive and accurate UV spectrophotometric method has been developed for the determination of gliclazide in bulk and pharmaceutical tablet dosage formulations. This method obeys Beer's law in the concentration range of 5 -30 μg/mL with correlation coefficient of 0.9956 and exhibiting maximum absorption

at 224 nm with apparent molar absorptivity of 0.1236×10^3 $Lmol^{-1}cm^{-1}$. The method is accurate and precise and is extended to pharmaceutical tablet dosage forms and there was no interference from any common pharmaceutical additives and excipients.[33]

18. Kathiresan K et al The present study was aimed to formulation and development of indomethacin sustained release tablets by wet granulation method. The main objective of this work is decrease the dosage frequency, to decrease dose dumping, increase the patient compliance and to enhance the desired activity by adopting the wet granulation technique. In this study, excipients are selected in four different concentrations (F-1, F-2, F-3, and F-4) and formulated by wet granulation method. Then all four formulations are evaluated. By observing the dissolution profile of trials, trial-4 (formulation-4) was better formulation of all the trails. In trial-4 indomethacin was formulated as sustained release tablets by using ethyl cellulose and HPMC k-100. And that having good dissolution profile for a controlled period of time which shown 83.4% at end of 12^{th} hour.[34]

19. Dr. Shivhare UD et al Once daily sustained release tablets of aceclofenac were formulated by wet granulation using carboxypolymethylene polymer. The drug excipient mixtures were subjected to preformulation studies while the tablets were subjected to physicochemical studies, *in vitro* drug release, stability studies and validation studies. Formulation F2 & F9 containing Carbopol 971P and Carbopol 974P were found to release the drug in sustained manner up to 24 hour and were stable under accelerated conditions of temperature for 6 months since there were no significant changes in drug content and physical parameters.[35]

20. Raghvendra rao NG et al Sustained release matrix tablets of water soluble tramadol hydrochloride using different polymers viz. hydroxy propyl

methyl cellulose (HPMC) and natural gums like karaya gum (KG) and carrageenan (CG). Varying ratios of drug and polymer like 1:1 and 1:2 were selected for the study. After evaluation of physical properties of tablet, the *in vitro* release study was performed in 0.1N HCl pH 1.2 for 2 hrs and in phosphate buffer pH 6.8 up to 12 hrs. The effect of polymer concentration and polymer blend concentration were studied.[36]

21. Patel R, et al Sustained release matrix tablet of theophylline were formulated by using different grades of hydroxypropyl methyl cellulose were evaluated for gel forming properties. The effects of polymers concentration on drug release profile were investigated. A 32 full factorial design was applied to systemically optimize the drug release profile. The amounts of HPMC K-4M (X1) and HPMC K-100M (X2) were selected as independent variables. Cumulative % release of drug for 1st hour and 8th hour were selected as dependent variables. The results of the full factorial design indicated that a low amount of HPMC K-100M and a high amount of HPMC K-4M favors sustained release of theophylline from matrix tablet.[37]

22. Hiremath P.S., et al Controlled release matrix tablet of Rifampicin and isoniazid combination, to study the design parameters and to evaluate in vitro release characteristics. In the present study, a series of formulations were developed with different release rates and duration using hydrophilic polymers hydroxypropyl methylcellulose (HPMC) and hydroxypropyl cellulose (HPC). The duration of rifampicin and isoniazid release could be tailored by varying the polymer type, polymer ratio and processing techniques. Further, Eudragit L100-55 was incorporated in the matrix tablets to compensate for the pH-dependent release of rifampicin.[38]

23. Savaser A et al The effects of formulation variables on the release profile of diclofenac sodium (DS) from hydroxyl propyl methyl cellulose (HPMC) and chitosan matrix tablets were studied. DS tablets were prepared by wet granulation and direct compression methods and different ratios of HPMC and chitosan were used. Physical properties of the prepared tablets and targeted commercial sustained release (SR) tablet and the drug release were studied in tablets that were placed in 0.1M HCl for 1 hr and phosphate buffer solution was added to reach pH value of 7.5. *In vitro* studies showed that 20% HPMC contained SR formulation with direct (dry) compression method is the optimum formulation due to its better targeting profile in terms of release.[39]

24. Toshiaki N et al The sustained-release tablet of sodium diclofenac (SR-tablet) was prepared simply by mixing sodium diclofenac with hydrogenated soya lecithin without any other additive. The dissolution of sodium diclofenac from the SR- tablet occurred in an apparent zero-order kinetics process with 90% release at 24 hr. The human subjects to whom the SR-tablet was administered excreted diclofenac in urine gradually up to 24 hr. However, they excreted diclofenac rapidly and no more excretion of diclofenac was observed 9 hr after administration of the conventional tablets.[40]

25. Lütfi G, et al Matrix tablets of ketorolac tromethamine (KT) were prepared by direct compression technique and Carbopol 934, 940 and 1342 have been used as polymers in different concentrations (5-15 %).The *in vitro* release kinetics of ten different formulations of KT matrix tablet were studied. According to our results, different types and concentrations of carbopol to tablet formulations may effect incontrolled drug release.[41]

26. Sasidhara RLC et al Verapamil HCl was formulated as an oral CR matrix tablets by using poly (ethylene oxides) {Polyox WSR 303 and Polyox WSR 301}. In this study, the matrix tablets were prepared by direct compression method. The drug release from the formulations followed first order kinetics and were linear with Higuchi plots. The *in vitro* drug release studies for different formulations were also compared with drug release studies of commercially available products. The results indicated that the formulations containing drug and polymer ratio 1:0.5 for Polyox WSR 303 and 1:1 for Polyox WSR 301 for Verapamil HCl were linear with drug release rates of marketed products. The formulations containing drug and polymer ratio 1:1, 1:1.5 for Polyox WSR 303 and 1:1.5 for Polyox WSR 301 showed greater inhibition on release rate of Verapamil HCl from the tablet matrix.[42]

27. Baveja SK et al Sustained release tablet dosage form of centperazine, a pale yellow viscous oily liquid, freely soluble in water and all common polar and non-polar solvents, was prepared using hydrophilic polymers as matrix materials. A formulation containing centperazine, Aerosil 200, sodium carboxy methyl cellulose (NaCMC) and hydroxyl propyl methyl cellulose (HPMC) in the ratio of 1: 0.7: 4: 4 was found to be the best in the study when tested in vitro and in vivo (man) giving linear release for about 12 hr. The release of drug from this formulation was found to be independent of hardness of tablet and pH of the dissolution medium.[43]

28. Pandey VP et al Diltiazem hydrochloride was formulated as sustained release tablet using hydroxy propyl methyl cellulose (methocel), ethyl cellulose and eudragit as sustaining materials in various proportions and differed in hardness. Study indicated that higherhardness slowed the release pattern in dissolution study**.** [45]

29. Patra CHN et al Controlled release formulation of propranolol hydrochloride using guar gum as a carrier and also to study the influence of some cellulose ethers like sodium carboxymethyl cellulose, hydroxy propyl methyl cellulose, hydroxy propyl cellulose and ethyl cellulose on the *in-vitro* release of propranolol hydrochloride from guar gum matrix tablets. *In-vitro* release studies indicated that 30% of guar gum and cellulose ethers were found to be effective in retarding the release of propranolol hydrochloride. [46]

30. Harrian, Ghaffari et al Different retardant polymers including carbopol 934P, hydroxy propyl methyl cellulose (HPMC K_4M) and eudragit NE 30 D, RL 30 D and RS 30 D as rate controlling materials were evaluated. The influence of variable including polymer type, drug: polymer ratio, tablet filler type and tablet hardness on isosorbide dinitrate release profile was discussed. From the retardant polymers investigated. Eudragit NE 300 D exhibited proper release characteristics.[47]

31. Farid DJ et al The effect of various polymers on the release of nifedipine from their matrix was evaluated. *In-vitro* release profile of nifedipine from eudragit RS matrix showed that increasing the concentration of eudragit RS resulted in reduction of the release rate of nifedipine.[48]

32. Hajare AA et al Diltiazem hydrochloride matrix tablets were fabricated by using of polymers like guar gum (GG), sodium carboxymethyl cellulose and hydroxy propyl methylcellulose (HPMC) polymers by wet granulation method and evaluated for various physical characteristics, drug polymer interaction and *in-vitro* drug release and for stability. The results were found that HPMC and GG were show excellent sustained release and found to follow zero order.[49]

33. Behl Ak et al Formulation of ofloxacin tablets by various polymers hydroxy propyl methyl cellulose K_4M, hydroxy propyl methyl cellulose E_5 and effect of lubricant was studied. Study showed that hydroxypropyl methyl cellulose is appropriate polymer and preparation of matrix by wet granulation was found to be more effective.[50]

34. Thapa P et al Study was carry out influence of different diluents,carbopol 934 P concentrations and granulation technique in the release of poorly water soluble drug (ibuprofen) from carbopol 934 P matrix tablets. A significant effect of granulation technique, polymer concentration in the drug release rate from carbopol 934P matrix based tablets was observed. Diluents had appreciable effect on drug release rate only at low polymer concentration.[51]

35.Mutalik S et al Once daily sustained release tablets of Aceclofenac were prepared by direct compression using hydroxyl propyl methyl cellulose-K_4 M (HPMC). By comparing the dissolution profiles with the marketed product, the tablet containing HPMC (45%) and microcrystalline cellulose (30%) along with talk and magnesium Stearate (1%w/w each) was considered as a better formulation.[52]

36. Tabandesh H et al Matrix tablets of aspirin were prepared using ethyl cellulose, eudragit RS100 (RS) and eudragit S100 (S) by direct compression. The release behavior were then studied in two counterpart series of tablets with varied hardness and compared by non-linear regression analysis. The studied indicated that ethyl cellulose with an amount as little as 10% was used to make sustained release aspirin tablets in which the release profile was not sensitive to moderate changes in hardness.[53]

37. Udupa N et al Sustained released tablets of salbutamol sulphate were prepared by granulation method using PVP K-30, EC, sodium CMC, eudragit L-100, eudragit RL-100, guar gum etc as rate controlling agent. The studied indicated that combination of eudragit and beeswax produce more prominent sustained action of salbutamol.[54]

38. Conti S et al Matrix tablets containing a soluble drug were prepared by using polymer hydroxy propyl methyl cellulose (HPMC) and sodium carboxy methyl cellulose (NaCMC) alone and in combination. To evaluated the effect of the dissolution medium at pH 1, 4.5 and 6.8. *In vitro* release studies showed that the mixture of the two cellulose derivatives enables a better control of the drug release profiles at pH 4.5 and at 6.8 both in term of rate and mechanism.[55]

39. Kiortsis S et al Four drugs differing in solubility (diclofenac sodium, ibuprofen, naproxen and indomethacin), two cellulosic polymers (HPC and HPMC) and hydrophobic Envelope were used in two levels of mass fraction and weight ratio of drug: carrier and of cellulosic–hydrophobic component. It was found that for the release mechanism most significant was the effect of drug solubility followed by cellulosic polymer type, mixing procedure and drug mass fraction. Depending on the drug solubility and type of polymer present, wet granulation can increase or decrease the release rate.[56]

40. Katikaneni PR et al Pseudoephedrine hydrochloride was used to prepare direct compression sustained release tablets with different viscosity grades of ethyl cellulose (EC). An increase in viscosity grade resulted in a marginal to moderate increase in the release

rate. However, lower viscosity grades produced harder tablets. The highly compressible 10 cp grade was used to study the effect of drug loading, particle size, compression force, and magnesium stearate concentration on release properties. The square of drug release decreased with a decrease in the drug concentration in the matrix.[57]

41. Sung KC et al Effect of two formulation variables, hydroxyl propyl methylcellulose (HPMC)/lactose ratio and HPMC viscosity grade, on the release of adinazolam mesylate drug and HPMC from HPMC-based matrix tablets was studied. Both drug and HPMC release were found to be a function of the formulation variables, with higher drug and HPMC release rates for formulations with lower HPMC/lactose ratios and lower HPMC viscosity grades. It was concluded that diffusion of drug through the hydrated gel layer was the predominant drug release mechanism for most of the formulations studied .[58]

42. Pather SI et al Sustained release theophylline tablets by direct compression by use of ethylcellulose were investigated. Matrices of this polymer display slow surface erosion which can be enhanced by the incorporation of a swelling agent. The theophylline to ethyl cellulose ratio and the tablet hardness were found to influence the rate of drug release.[59]

43. Gil EC et al The sustained-release matrix tablets of propranolol hydrochloride (PPL) were prepared by polymer like native dextran, hydroxyl propyl methylcellulose (HPMC), cetyl alcohol alone and binary mixtures of them and release *in-vitro* was investigated. The sustained-release matrix tablets were obtained with matrix excipients: PPL ratio of 60:40 (w/w), with a dextran: HPMC ratio of 4:1 (w/w) and with a cetyl alcohol amount of 15% (w/w).

A comparative kinetic study of the present matrix tablets and commercial sumial retard capsules was established. The value for the similarity factor suggested that the dissolution profile of the present two sustained-release oral dosage forms were similar.[60]

44. Huang YB, et al Once-daily extended release propranolol matrix tablets were formulated containing HPMC, microcrystalline cellulose (MCC) and lactose. The *in-vitro* studies were carried out by surface methodology and polynomial equation. The results showed that the mechanism of drug release from HMPC matrix tablets followed non-Fickian diffusion.[61]

MATERIALS & METHODS

The following materials that were either AR/LR grade or the best possible pharma grade available were used as supplied by the manufacturer.

TABLE No- 1.MATERIALS USED

MATERIALS	**GRADE**	**COMPANY**
Gliclazide	Pharma	Zhejiang Jiuzhou Pharmaceuticals Co., Ltd. China.
HPMC K4M	Pharma	Colorcon asia Pvt.Ltd.
HPC 75-100	A.R.	Twilight Litaka Pvt Ltd. Pune.
Di-calcium Phosphate	--	Enar Chem.
Pvp K_{30}	L.R.	ISP tech inc.
Magnesium Stearate	A.R.	Sunshine Organics.
Aerosil	A.R.	Cabot sanmar.

Table No – 2. INSTRUMENTS AND EQUIPMENTS USED

S.No	Instruments/Equipments	Company
1.	Electronic balance	Shimadzu
2.	Hardness tester	Incorp.
3.	Friability test apparatus	Roche Friabilator
4.	Hydraulic press	Rimek Mini Press – 1
5.	Vernier	Ayesh.
6.	Tablet dissolution tester (USPXX III)	Electro Lab
7.	Density Tap tester	Electro Lab
8.	UV Spectrophotometer	Shimadzu
9.	FTIR Spectrophotometer	Shimadzu
10.	pH meter	Contech.
11.	Humidity chamber	Thermo Lab.
12.	Coating machine	Biochem.
13.	HPLC	Shimadzu
14.	Hot air oven	Tempo Instruments and Equipments (I) Pvt. Ltd.

METHODS

I. Preparation of calibration curve.

1) Preparation of standard graph of Gliclazide using Phosphate buffer pH 7.4

II. Compatibility studies.

III. Evaluation of Pre-compression parameters.

IV. Formulation of tablets of Gliclazide.

1) Preparation of sustained release matrix tablets of Gliclazide with HPMC

2) Preparation of sustained release matrix tablets of Gliclazide with HPC.

3) Preparation of sustained release matrix tablets of Gliclazide with HPMC & HPC.

V. Composition of Matrix tablets of Gliclazide

VI. Evaluation of the prepared formulation for Physico-Chemical characteristics.

VII. *In-vitro* drug release studies using phosphate buffer pH 7.4.

VIII. Determination of assay and relative substances

IX. Data analysis (curve fitting analysis).

X. Stability studies.

I. PREPARATION OF CALIBRATION CURVE [14].

1). Preparation of standard graph of Gliclazide using phosphate buffer pH 7.4.

Beer's law is obeyed in the concentration range of 5 – 25 mcg/ml.

Method:-

50 mg of Gliclazide was accurately weighed into 100ml volumetric flask and dissolved in phosphate buffer pH 7.4. The volume was made up to 100ml to get a concentration of (0.5 mg/ml.) stock solution- I. From this, 1 ml was withdrawn and diluted to 10 ml to get a concentration of (25 µg/ml) stock solution -II.

Scanning of Drug:-

From stock solution-II (SS-II), 4 ml was withdrawn and the volume was made up to 10 ml with phosphate buffer pH 7.4 to get a concentration of 10 µg/ml. UV scan range was taken between the wavelengths 200-400 nm. It gave a peak at 226 nm and 290 nm and the same was selected as λ_{max} for Gliclazide.

Calibration curve in phosphate buffer pH 7.4:-

From the standard stock solution-II (SS-II) 2, 4, 6, 8 and 10 ml were withdrawn and volume ware made up to 10 ml with phosphate buffer pH 7.4 to give a concentration of 5, 10, 15, 20 and 25 µg/ml. Absorbance of these solutions ware measured against a blank of phosphate buffer pH 7.4 at 266 nm and 290 nm for Gliclazide and the absorbance values ware summarized in Table 5. Calibration curve was plotted, drug concentrations versus absorbance was given in the Fig. 14.

II. DRUG-EXCEPIENTS COMPATIBILITY STUDIES BY FTIR.

Excipients are integral components of almost all pharmaceutical dosage forms. The successful formulation of a stable and effective solid dosage form depends on the careful selection of the excipients, which are added to facilitate administration, promote the consistent release and bioavailability of the drug and protect it from degradation.

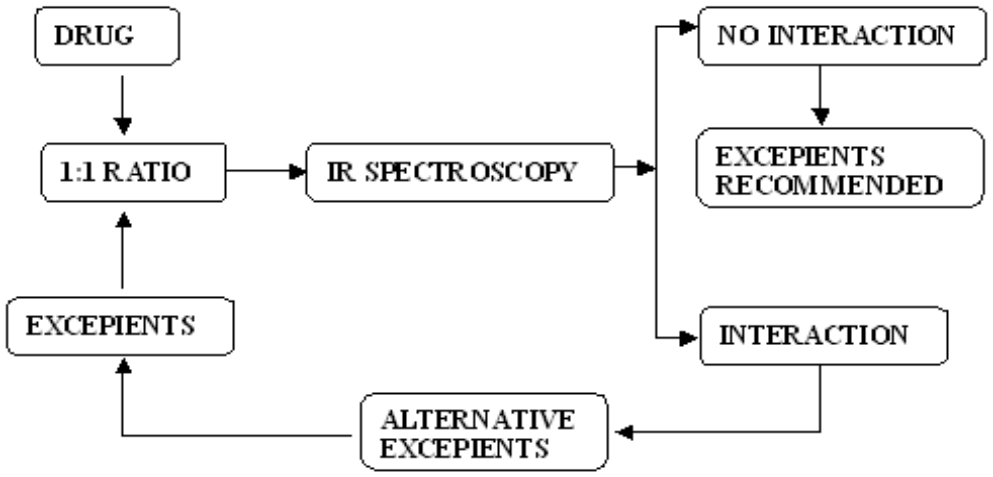

Fig no-10 Schematic representation of compatibility studies

Infra Red spectroscopy is one of the most powerful analytical techniques to identify functional groups of a drug.

Method: -

The pure drug and its formulation were subjected to IR studies. In the present study, the potassium bromide disc (pellet) method was employed.

III. EVALUATION OF PRE-COMPRESSION PARAMETER.[17]

1) Angle of Repose (θ):-

This is the maximum angle possible between the surface of a pile of powder or granules and the horizontal plane.

The powders were allowed to flow through the funnel fixed to a stand at definite height (h). The angle of repose was then calculated by measuring the height and radius of the heap of granules formed.

$$\tan \theta = h/r \quad \theta = \tan^{-1} (h/r)$$

Where, θ = angle of repose

h = height of the heap

r = radius of the heap

Table no-3The relationship between Angle of repose and powder flow

Angle of repose	Powder flow
< 25	Excellent
25-30	Good
30-40	Passable
> 40	Very poor

2) Compressibility Index:-

The flow ability of powder can be evaluated by comparing the bulk density (Do) and tapped density (D_f) of powder and the rate at which it packed down. Compressibility index is calculated by –

Compressibility index (%) = $\frac{D_f - D_o}{D_f} \times 100$

Where Do = Bulk density
D_f = Tapped density

Table no-4The relationship between Percent compressibility and Type of flow

Percent compressibility	Type of flow
5-15	Excellent
12-16	Good
18-21	Fare-passable
23-25	Poor
33-38	Very poor
>40	Extremely poor

3) Hausner's ratio: -

It is the ratio of tapped density to bulk density.

Hausner's ratio = D_f / Do

Where Do = Bulk density
D_f = Tapped density

4) Content Uniformity: -

The granules were crushed and power containing 100 mg of Gliclazide was dissolved in 100 ml of methanol. The solution was passed through a whatmann (No. 1) filter and analyzed spectrophotometrically at 226 nm and 290 nm after sufficient dilution with distilled water.

IV. FORMULATION OF MATRIX TABLETS OF GLICLAZIDE.[80]

1). Preparation of sustained release matrix tablets of Gliclazide with HPMC/HPC or both retarding material.

- Weigh and shift the Gliclazide, Di-Calcium phosphate through mesh # 40.
- Weigh the PVP K-30 and dissolve in water by means of mechanical stirrer.
- Dry mix the step one material in planetary mixer for 10 min.
- Add the above binder solution into it with in 2-3 min run the planetary mixer at slow speed for 8-10 min and at high speed for 2-3 min. Add extra water if require.
- Semidry granules at 60 ^{0}C for 30-40 min, passed through mesh #20, again dry it till LOD (2-3%).
- Weigh the HPC 75-100, HPMC K-4M, magnesium stearate and aerosol passed through mesh #40.
- Lubricate it for 5 min with step 4 blend and check the blend parameter.
- Compressed tablet using punch size 10 mm with 16 station compressed machine.
- And finally check in process parameter.

V. Table No.5. Composition of Matrix tablets of Gliclazide.

Ingredients (mg/tablet)	**F_1**	**F_2**	**F_3**	**F_4**	**F_5**	**F_6**	**F_7**	**F_8**	**F_9**
Gliclazide	60	60	60	60	60	60	60	60	60
HPC 75-100	60	70	80	---	---	---	30	30	30
HPMC K4M	---	---	---	60	70	80	30	40	50
Di-calcium Phosphate	215	205	195	215	205	195	215	205	195
$PvpK_{30}$	10	10	10	10	10	10	10	10	10
Magnesium Stearate	4	4	4	4	4	4	4	4	4
Aerosil	1	1	1	1	1	1	1	1	1
Water	q.s.	q.s.	q.s.	q.s.	q.s.	q.s.	q.s.	q.s.	q.s.
Total weight	350	350	350	350	350	350	350	350	350

VI. EVALUATION OF THE PREPARED FORMULATION FOR PHYSICO-CHEMICAL CHARACTERISTIC.[17]

All prepared matrix tablets were evaluated for the following parameters.

1) Shape of Tablets:-

Tablets were examined under the magnifying lens for the shape of the tablet.

2) Tablet Dimensions: -

Thickness and diameter were measured using a calibrated vernier caliper. 3 tablets of each formulation were picked randomly and thickness was measured individually.

3) Weight variation: -

The causes for weight variation can be divided into granulation and mechanical problems. If the granule size is large, the dies will not be uniformly filled. Similarly mechanical problems can be traced of lower punches of non-uniform length.

Method: - Uncoated tablets complies this test. The average weight is determined by weighing 20 tablets. Not more than two tablets deviate from the average weight by a percentage greater than that given and no tablet deviates by more than double that percentage. Weight variation tolerances for uncoated tablets:

Table no-6 The allowed weight variation of tablets

Average Weight of Tablets (mg)	Maximum Difference Allowed (%)
130 or less	10
130-324	7.5
More than 324	5

4) Hardness: -

Hardness was measured using Incorp Hardness tester that measures the pressure required to break diametrically placed matrix tablets by applying pressure with coiled spring.

5) Friability: -

The friability of tablets was determined by using Roche friabilator. It is expressed in percentage (%). 6 tablets were initially weighed ($W_{initial}$) and transferred into friabilator. The friabilator was operated at 25 rpm for 4 minutes or run up to 100 revolutions. The tablets were weighed again (W_{final}). The % friability was then calculated by-

$$\%F = 100\ (1\text{-}W_0/W)$$

% Friability of tablets less than 1% was considered acceptable.

6) Drug Content: -

The drug content, 1 tablet was crushed and powder containing 100 mg of Gliclazide was dissolved in 100 ml of distilled water. The solution was passed through a whatmann (No. 1) filter and analyzed spectrophotometrically at 226 nm and 290 nm after sufficient with distilled water.

7) Swelling Study:

The swelling behavior of a dosage form was measured by studying its weight gain or water uptake. The dimensional changes could be measured in terms of the increase in tablet diameter and/or thickness over time. Water uptake was measured in terms of percent weight gain, as given by the equation.

$$WU = \frac{(W_t - W_0)\ X\ 100}{W_0}$$

W_t = Weight of dosage form at time t.

W_0 = Initial weight of dosage form

VII. *IN-VITRO* DRUG RELEASE STUDIES USING PHOSPHATE BUFFER pH 7.4.[14]

Theoretically, an *in-vitro* test for drug availability should measure in reality the physical phenomenon controlling availability *in-vivo*. This is not feasible for orally administered dosage forms because G.I fluids are not constant in composition and the dosage form moves at some unknown rate through the number of fluids. It is not possible to simulate a single test system which would incorporate reflection of all such variables as interaction between drugs and constituents, changes in volume, retention time, transit time and various other levels of agitation.

However *in-vitro* test can be carried out which will indicate the effects of these variables on the mechanism and kinetics of drug release from a dosage form. This will give an idea of how the dosage form will behave when subjected to *in-vivo* studies.

Determination of Dissolution Pattern: -

Freshly prepared test media of 900 ml was placed in dissolution vessels of dissolution test apparatus USP XXIV model. Six samples of the matrix tablet of Gliclazide (after weighing) was placed in 6 different jar containing dissolution media and temperature was maintained at 37.5 $\pm 1^0$C and paddle was rotated at the speed of 100 rpm. At the specified time interval withdraw 5 ml sample solution from each vessel and filter. Further dilute the sample upto 25ml with dissolution medium.

Then measure the absorbance of standard and sample solution in 1 cm cell on a suitable UV spectrophotometer at 226 nm and 290 nm, using dissolution as blank. Correct the absorbance obtained at 226 nm by subtracting the absorbance obtained at 290 nm. Record the absorbance and calculate the percentage of Gliclazide dissolved in dissolution media by using following formula.

$$\text{Drug release} = \frac{\text{Conc. of Gliclazide x Dilution Factor x Dissolution medium}}{1000}$$

$$\% \text{ of Drug release} = \frac{\text{Drug release}}{\text{Dose of Drug}} \times 100$$

Dissolution studies were performed for all formulations. The mean values and standard deviations were calculated.

VIII) Determination of Assay and Related Substances.[14]

1) Assay by HPLC: -

Reagents: -

- Acetonitrile : HPLC grade
- Triethylamine : HPLC grade
- Trifluroacetic acid : HPLC grade
- Water : Water for injection

Chromatographic condition: -

Column : Hypersil MOS1 C8 (250 x 4.6 mm, 5µ)

Pump Mode : Isocratic

Flow Rate : 0.9 ml/min

Detection : UV, at 235 nm

Column temperature : Ambient

Injection volume : 20 µl

Autosampler : 5^0C

Preparation of Mobile Phase: -

Add 450 ml of Acetonitrile to the 550 ml of Water and mix well. With condition stirring add 1ml of Triethylamine and 1ml of Trifluroacetic acid.

Preparation of diluents 1: -

Add 400 ml of Acetonitrile into 600 ml of water and mix well.

Preparation of Solution: -

Sample Solution: -

Weigh about quantity of the powdered tablets equivalent 200 mg of Gliclazide from 20 tablets into 50 ml of volumetric flask, and add 30 ml of Acetonitrile mix well and sonicate for 30 minutes and allow to cool at room temperature and make up the volume with Acetonitrile and mix well. Filter the solution through nylon filter paper 0.45 µ and transfer this 5 ml to 100 ml volumetric flask and make up the volume with Diluent and mix well.

Standard Solution: -

Weigh about 40 mg of Gliclazide standard into 200 ml volumetric flask. Dissolve in 30 ml of Acetonitrile, sonicate for 5 minutes and make up the volume with Diluent and mix well.

Evaluation of system suitability:-

Inject 20 µl of Standard solution five times in to the chromatograph and measure the Gliclazide peak areas. RSD for five replicates injections of standard solutions is not more than 2.0%.

Procedure: -

Inject 20µl of blank, Standard solution and sample solution into the chromatograph, record the chromatograms.

Calcualtion for tablets: -

$$\text{Content of Gliclazide } (C_{15}H_{21}N_3O_3S) \text{ mg per tablet} = \frac{T_A \times D_S \times P \times N}{S_A \times D_T \times 100}$$

Where,

TA = Average area counts of sample solution

SA = Average area counts of five replicate injection for Gliclazide peak in the chromatograms of standard solution.

DS = Dilution factor of standard solution (weight / Dilution)

DT = Dilution factor of sample solution (weight / Dilution)

P = Percent purity of Gliclazide standard

N = Average weight of the tablet.

2) Related substances: -

Preparation of Diluent 1: -

Add 450 ml of Acetonitrile into the 550 ml of water and mix well.

Preparation of Diluent 2: -

Add 300 ml of Acetonitrile into the 600 ml of water and mix well

Preparation of sample solution: -

Weigh about quantity of powdered tablets equivalent 200 mg of Glicalzide (from 20 tablets) into 50 ml of volumetric flask, and add 30 ml of Acetonitrile mix well and sonicate it for 30 minutes allow cooling at room temperature and making up the volume with Acetonitrile and mixing well. Filter the solution through nylon filter paper 0.45µ and transfer this 10 ml to 50 ml volumetric flask and make up the volume with Diluent 2 and mix well.

Placebo preparation: -

Weigh about quantity of the 934 mg of placebo to 50 ml of volumetric flask, and add 30 ml of Acetonirile mix well and sonicate for 30 minutes allow cooling at room temperature and making up the volume with

Acetonirile and mixing well. Filter the solution through nylon filter paper 0.45µ and transfer this 10 ml to 50 ml volumetric flask and make up the volume with Diluent 2 and mix well.

Standard Solution: -

Weigh accurately about 40 mg of Gliclazide standard into 200 ml volumetric flask. Dissolve in 10 ml of Acetonitrile, and make up the volume with Diluent 1. Dilute 2 ml of this solution to 200 ml of volumetric flask and make up the volume with Diluent 1.

Procedure: -

Inject 20µl of blank, placebo standard solution and sample solution; measure peak response and calculate.

Calculation: -

Total impurities: $$\frac{A_{T1} \times D_C \times P \times 100 \times N}{A_C \times D_T \times 100 \times L}$$

Where,

A_{T1} = Area count of Single maximum impurity peak in the chromatogram of sample

A_C = Area count of Gliclazide peak in the chromatogram of standard solution

D_C = Dilution factor for the standard solution (weight / dilution)

D_T = Dilution factor for the sample solution (weight / dilution)

P = Percent potency of Gliclazide working standard used

N = Average weight of the tablets

L = Lable claim of Gliclazide

IX) Data Analysis (*Curve Fitting Analysis*). [25, 34]

To analyze the mechanism of the drug release rate kinetics of the dosage form, the data obtained were graphed as:

1) Cumulative percentage drug released Vs Time (In-Vitro drug release plots)
2) Cumulative percentage drug released Vs Square root of time (Higuchi's plots)
3) Log cumulative percentage drug remaining Vs Time (First order plots)
4) Log percentage drug released Vs Log time (Peppas plots)

- ***Higuchi release model: -***

To study the Higuchi release kinetics, the release rate data were fitted to the following equation.

$$F = K \cdot t_{1/2}$$

Where, 'F' is the amount of drug release,

'K' is the release rate constant, and

't' is the release time.

When the data is plotted as accumulative drug released versus square root of time, yields a straight line, indicating that the drug was released by diffusion mechanism. The slope is equal to 'K'.

- ***Korsmeyer and Peppas release model: -***

The release rate data were fitted to the following equation,

$$M_t / M_\infty = K \cdot t^n$$

Where, M_t / M_∞ is the fraction of drug release,

'K' is the release constant,

't' is the release time, and

'n' is the diffusional exponent for the drug release that is dependent on the shape of the matrix dosage form.

When the data is plotted as Log of drug released versus Log time, yields a straight line with a slope equal to 'n' and the 'K' can be obtained from Y- intercept.

For non-Fickian release the 'n' values falls between 0.5 and 1.0, while for Fickian (case I) diffusion n=0.5 and zero order release (case II transport) n=1.0.

- ***Zero order release rate kinetics: -***

To study the zero–order release kinetics the release rate data are fitted to the following equation.

$$F = Kt$$

Where 'F' is the fraction of drug release,

'K' is the release rate constant and

't' is the release time.

When the data is plotted as cumulative percent drug release versus time, if the plot is linear then the data obeys zero-order release kinetics, with a slope equal to K.

- **First Order Kinetics:**

A first order release would be predicated by the following equation.

$$\text{Log } C = \log Co - \frac{Kt}{2.30}$$

Where; C = Amount of drug remained at

time‘t’ Co = Initial amount of drug

K = First order rate constant (hr^{-1})

When the data is plotted as cumulative percent drug remaining versus time yields a straight line, indicating that the release follows First-order kinetics. The constant ‘k’ can be obtained by multiplying 2.303 with slope values.

X) STABILITY STUDIES.[89, 90]

1. Introduction: -

In any rational drug design or evaluation of dosage forms for drugs, the stability of the active component must be a major criterion in determining their acceptance or rejection.

Stability of a drug can be defined as the time from the date of manufacture and the packaging of the formulation, until its chemical or biological activity is not less than a predetermined level of labeled potency and its physical characteristics have not changed appreciably or deleteriously.

2. Objective of the Study.

The purpose of stability testing is to provide evidence on how the quality of a drug substance or drug product varies with time under the influence of a variety of environmental factors such as temperature, humidity and light, enabling recommended storage conditions, re-test periods and shelf-lives.

Long-term Testing: 25^0 C ± 2^0 C / 60 % RH ± 5 % for 12 Months.

Accelerated Testing: 40^0 C ± 2^0 C / 75 % RH ± 5 % for 6 Months.

The International Conference on Harmonization (ICH) Guidelines titled "Stability Testing of New Drug substance and Products" (QIA) describes the stability test requirements for drug registration applications in the European Union, Japan and the United States of America.

ICH specifies the length of study and storage conditions.

Stability studies were carried out at 25^0 C / 60 % RH and 40^0 C / 75 % RH for the selected formulation for the period of 3 months.

Method: -

The selected formulations were packed in amber-colored bottles, which were tightly plugged with cotton and capped. They were then stored at 25^0 C / 60% RH and 40^0 C / 75 % RH for 3 months and evaluated for their physical appearance, drug content and drug excipients compatibility at specified intervals of time.

RESULTS & DISCUSSION

I. CALIBRATION CURVE.

Standard Calibration Curve of Gliclazide in phosphate buffer pH 7.4:-

Standard calibration curve of Gliclazide was drawn by plotting absorbance v/s concentration. The absorbance values are tabulated in Table 6. Standard calibration curve of Gliclazide in the Beer's range between 5-25 µg/ml is shown in Fig.11

Table No. 7. Calibration data of Gliclazide in phosphate buffer pH 7.4 at 226 nm and 290 nm.

SL. No.	Concentration (µg/ml)	Absorbance*
1	0	0
2	5	0.108
3	10	0.224
4	15	0.339
5	20	0.423
6	25	0.552

*Average of 3 determinations

The linear regression analysis for standard curve in phosphate buffer pH 7.4:-

The linear regression analysis was done on absorbance data points. The results are as follows:

The Slope = 0.022

The intercept = 0 .002

The correlation coefficient = 0.996

A straight-line equation (y = mx + c) was generated to facilitate the calculation for amount of drug. The equation is as follows.

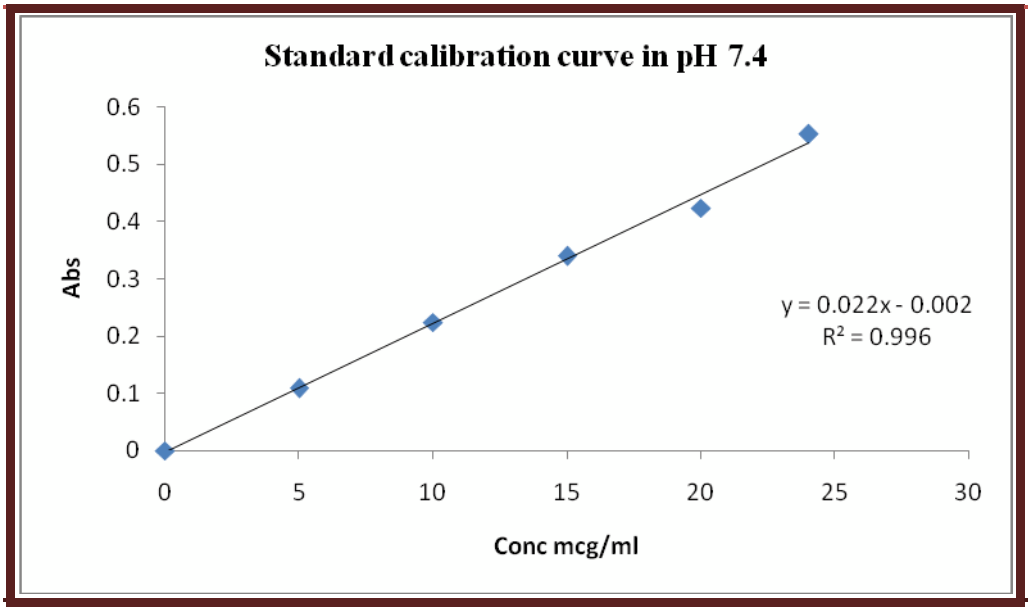

Fig.11: Standard calibration curve for Gliclazide in phosphate buffer pH 7.4 at 226 nm and 290 nm.

Absorbance = 0.022 x Concentration

II COMPATIBILITY STUDY:-

Compatibility studies were performed using IR spectrophotometer. The IR spectrum of pure drug and physical mixture of drug and polymer were studied making a KBr disc. The characteristic absorption peaks of Gliclazide were obtained at different wave numbers in different samples.

The peaks obtained in the spectra of each formulation correlates with the peaks of drug spectrum. This indicates that the drug is compatible with the formulation components. The spectra for all formulations are shown below.

The spectral details for all types of formulations are shown as follows

Table no 8- FTIR values in Pure drug Gliclazide.

	S.No	(KBr Disc) peaks at	Indications
IR Spectrum	1.	3272 cm^{-1}	NH, str.
	2.	3118 cm^{-1}	CH, str Ar
	3.	2931 cm^{-1}	CH str. CH_3
	4.	1708 cm^{-1}	C=O str.
	5.	1438,1352 cm^{-1}	C=C str.
	6.	1163 cm^{-1}	C-N str

Table no 9- FTIR values in Gliclazide + HPC 75-100

	S.No	(KBr Disc) peaks at	Indications
IR Spectrum	1.	3771 - 3190 cm^{-1}	NH, str.
	2.	2939 cm^{-1}	CH, str. CH_3
	3.	1708 cm^{-1}	C=C, str,
	4.	1436, 1348 cm^{-1}	C=C, str
	5.	1160, cm^{-1}	C- N str

Table no 10 - FTIR values in Gliclazide + HPMC

	S.No	(KBr Disc) peaks at	Indications
IR Spectrum	1.	3272 cm^{-1}	NH, str
	2.	3116 cm^{-1}	CH, st. Ar
	3.	2935 cm^{-1}	CH str, CH_3
	4.	1708 cm^{-1}	C=O, str
	5.	1596, 1436 cm^{-1}	C=C str
	6.	1163 cm^{-1}	C-N str

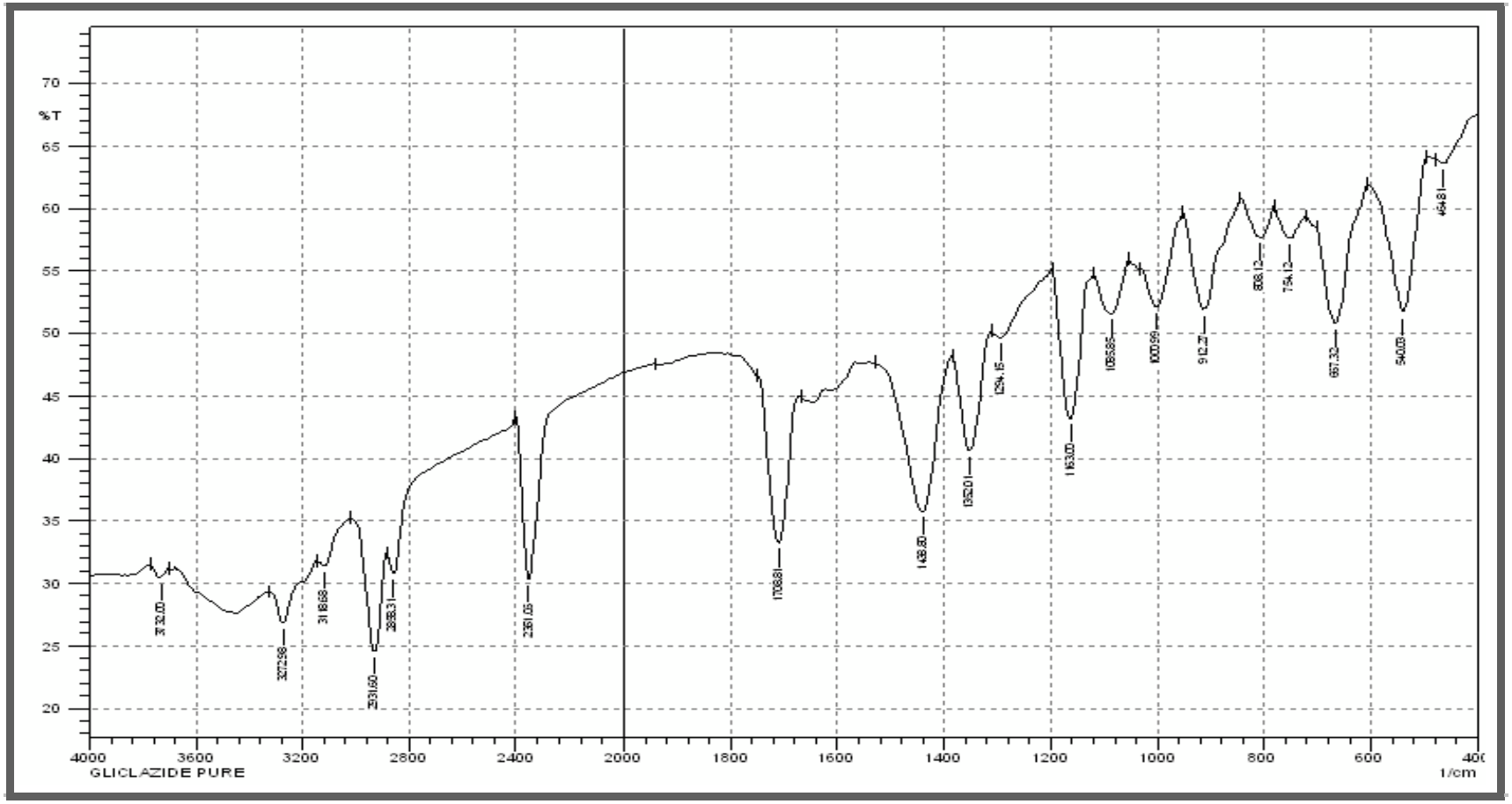

Fig. No-12: IR Spectrum of Gliclazide Pure Drug

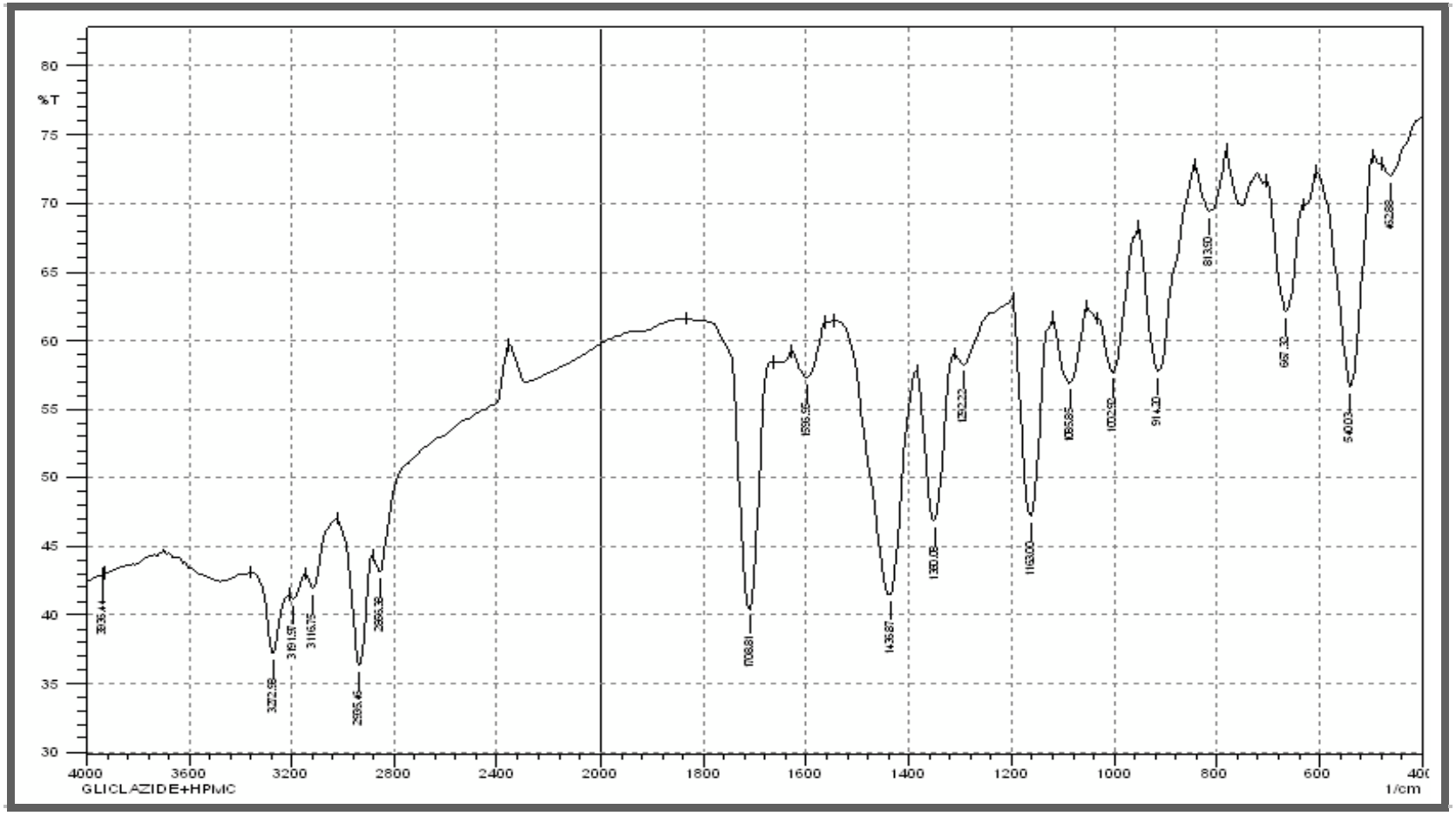

Fig.No-13: IR Spectrum of Gliclazide + HPMC K4M

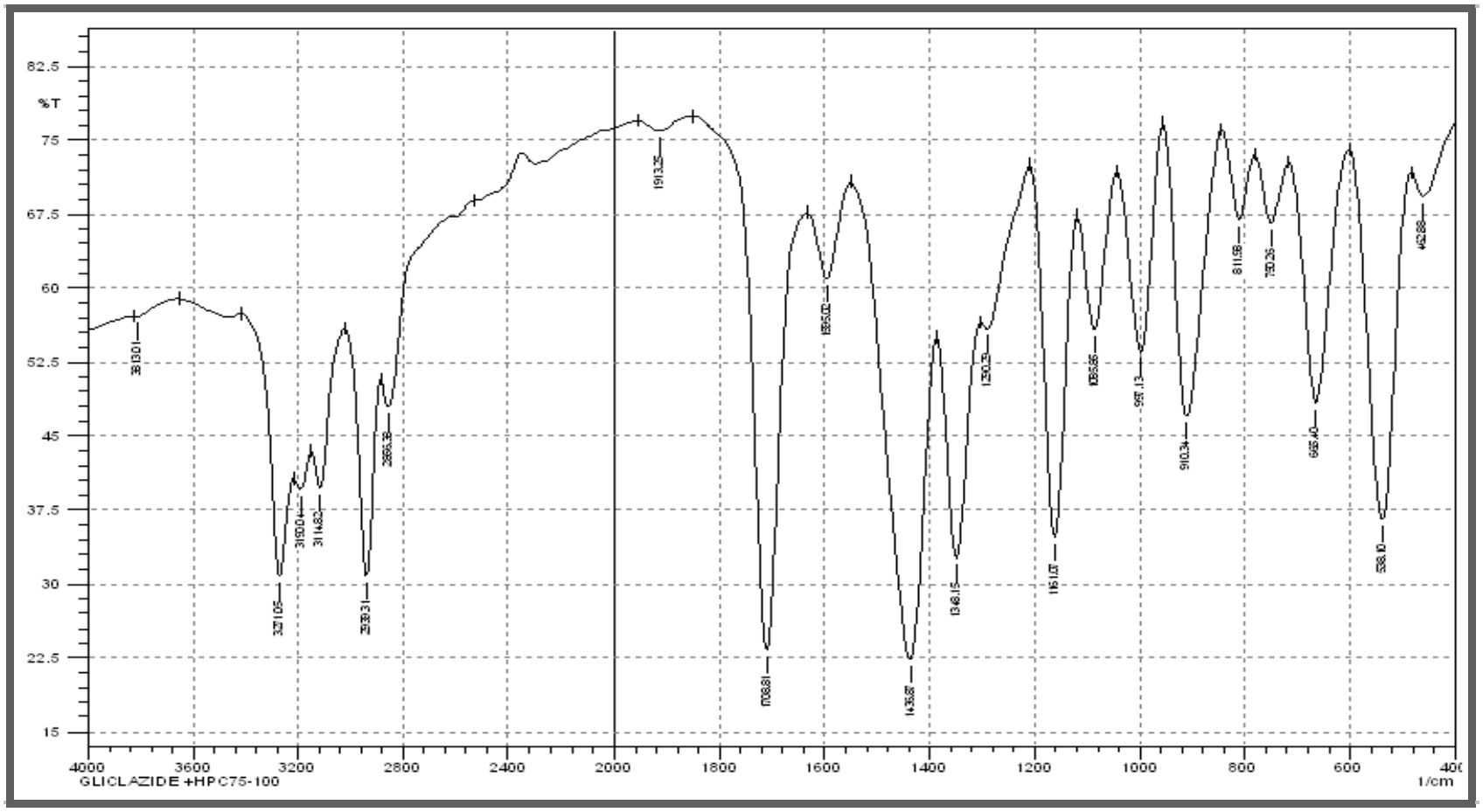

Fig. No-14: IR Spectrum of Gliclazide + HPC 75-100

Table No. 11: Physical Properties of all granules

Formulations	Angle of repose (θ)	Compressibility Index or Carr's Index (%)	Hausner's ratio	Drug uniformity* (%)
F_1	$28^0.95'$	15.15	1.178	98.94±0.40
F_2	$29^0.56'$	15.38	1.182	97.31±0.32
F_3	$25^0.94'$	16.42	1.196	99.75±0.33
F_4	$23^0.96'$	16.92	1.204	96.31±0.41
F_5	$24^0.14'$	16.42	1.196	98.69±0.22
F_6	$25^0.91'$	16.67	1.2	99.75±0.34
F_7	$22^0.69'$	14.28	1.167	99.75±0.21
F_8	$23^0.58'$	16.67	1.2	98.94±0.25
F_9	$25^0.95'$	14.92	1.175	99.75±0.34

***mean±SD, n=3.**

V. Table No. 12: Physical Properties of all Formulations.

Formulations	Diameter* (mm)	Thickness* (mm)	Weight variation# (mg)	Hardness* (kg /cm^2)	Friability (%)	Drug content* (%)
F_1	10.05±0.030	4.45±0.11	351±5	5.1 ± 0.12	0.191	97.00±0.24
F_2	10.06±0.040	4.50±0.04	350±5	5.5 ± 0.24	0.290	98.90±0.22
F_3	10.04±0.030	4.49±0.05	354±5	5.8 ± 0.21	0.146	97.86±0.34
F_4	10.02±0.030	4.45±0.12	345±5	5 .2± 0.23	0.149	98.75±0.32
F_5	10.02±0.054	4.46±0.03	347±5	5.9 ± 0.12	0.145	96.26±0.46
F_6	10.05±0.064	4.54±0.23	351±5	6.1 ± 0.14	0.191	98.45±0.26
F_7	10.07±0.022	4.52 ±0.2	352±5	5.2 ± 0.18	0.193	98.00±0.28
F_8	10.05±0.035	4.51±0.12	349±5	5.4 ± 0.22	0.146	99.72±0.30
F_9	10.04±0.059	4.53 ±0.3	348±5	6 .1± 0.21	0.191	98.82±0.34

* mean ±SD, n=6. # mean ±SD, n=20.

III. EVALUATION OF PRE-COMPRESSION PARAMETER.

1. Pre-compression Parameters.

1) Angle of repose (θ): -

The values obtained for angle of repose for all (F_1-F_9) formulations are tabulated in Table.6. The values were found to be in the range from 22^0.69′ - 29^0.56'.This indicates good flow property of the granules.

2) Compressibility index: -

The values obtained for compressibility index for all (F_1-F_9) formulations are tabulated in Table.6. Compressibility index value ranges between 14.28% - 16.92% indicating that the granules have the required flow property for compression.

3) Hausner's ratio: -

The values obtained for hausner's ratio for all (F_1-F_9) formulations are in Table.6. Hausner's ratio value ranges between 1.167 - 1.2 indicating that the granules have the required flow property for compression.

4) Drug uniformity: -

The percentage of drug uniformity was found to be between 96.31 % - 99.75 % of Gliclazide, which was within acceptable limits. Table.6. showed the results of drug content uniformity in each batch.

2. Post-compression Parameters.

1) Shape of the tablet: -

Microscopic examination of tablets from each formulation batch showed circular shape with no cracks.

2) Tablet dimensions: -

The dimensions determined for formulated tablets were tabulated in Table.7. Tablets mean thicknesses were almost uniform in all the formulations and were found to be in the range of 4.45 mm – 4.54 mm. The diameter of the tablet ranges between
10.02 mm – 10.07 mm.

3) Weight variation Test: -

The percentage weight variation for all formulations was shown in Table.7. All the tablets passed weight variation test as the % weight variation was within the Pharmacopoeial limits. The weights of all the tablets were found to be uniform with low standard deviation values

4) Hardness test: -

The measured hardness of tablets of each batch was in Table.7 and it was range between 5.1 kg/cm^2 - 6.1 kg/cm^2. Tablet hardness was increased as increasing the compression force. This ensures good handling characteristics of all batches.

5) Friability test: -

The values of friability test were tabulated in Table.7. The % friability was
NMT 1% in all the formulations ensuring that the tablets were mechanically stable.

6) Drug content: -

The percentage of drug content was found to be between 97.00 % - 99.72 % of Gliclazide, which was within acceptable limits. Table no.7 showed the results of drug content uniformity in each batch.

7) Swelling index: -

Swelling index of all formulations is shown in table no.8 and Fig no.18, 19 & 20 as time increases the swelling index was increased, because weight gained by tablet was increased proportionally with the rate of hydration up to 3 hours, 4 hours for HPMC and HPC respectively. Later on it decreases gradually due to dissolution of outermost gelled layer of tablet into dissolution medium. The direct relationship was observed between Swellin indexand polymer concentration, as polymer concentration increases, swelling index was increased. Comparison between HPMC and HPC. It has been observed that swelling index is more in HPMC followed by HPC. It was observed that cumulative % drug release decrease with increasing concentration of polymer and swelling index.

Table. No .13: Swelling Index Behavior Study of selected Formulations*

Time	F1	F2	F3	F4	F5	F6	F7	F8	F9
0	0	0	0	0	0	0	0	0	0
1	12.5	15.45	17.56	27.2	39.2	48.32	14.3	31.21	42.76
2	18.3	22.34	24.34	42.6	61.34	72.21	20.09	41.4	55.34
3	21.78	27.14	30.4	55.2	77.34	93.32	28.34	53.8	65.76
4	23.34	31.98	36.87	53.2	75.03	87.23	35.67	65.5	79.3
5	27.34	36.45	41.34	49.2	65.03	83.32	33.21	63.3	77.9
6	29.56	38.67	48.14	45.01	59	79.24	29.4	57.6	72.4
7	25.23	33.4	45.87	33.01	54.02	68.21	27.23	53.4	63.45
8	19.9	28.3	41.76	25.03	48.23	62.1	26.34	48.43	57.98
9	16.45	25.9	38.56	19.14	42.21	54.21	24.8	39.23	51.23
10	13.6	19.34	32.4	15.09	33.8	47.28	23.8	36.45	42.8
11	10.34	14.34	26.5	14.06	24.27	41.09	20.35	32.2	34.54
12	8.45	11.1	22.8	12.08	19.2	37.4	19.23	27.4	31.4

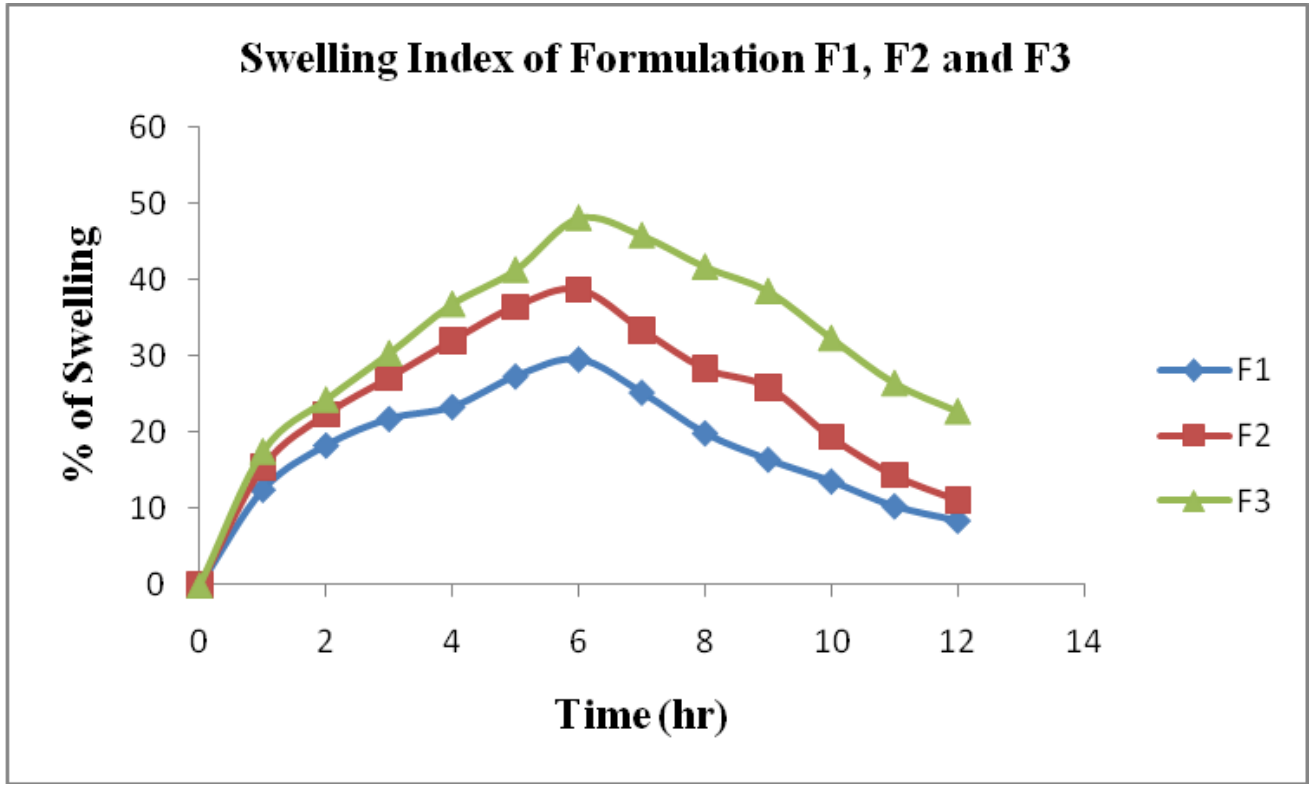

Fig no-15 Swelling Index of Formulations F1,F2 and F3

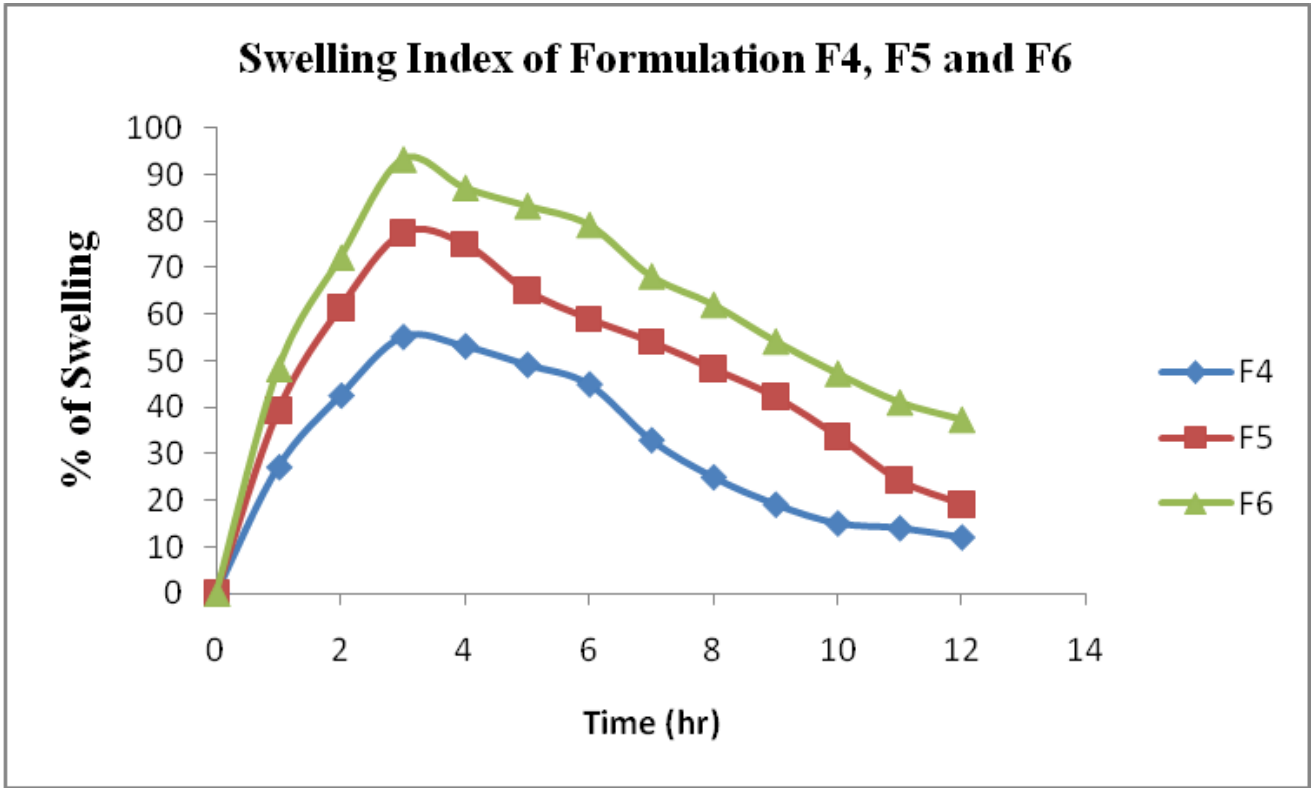

Fig no.16 Swelling Index of Formulations F4,F5 and F6

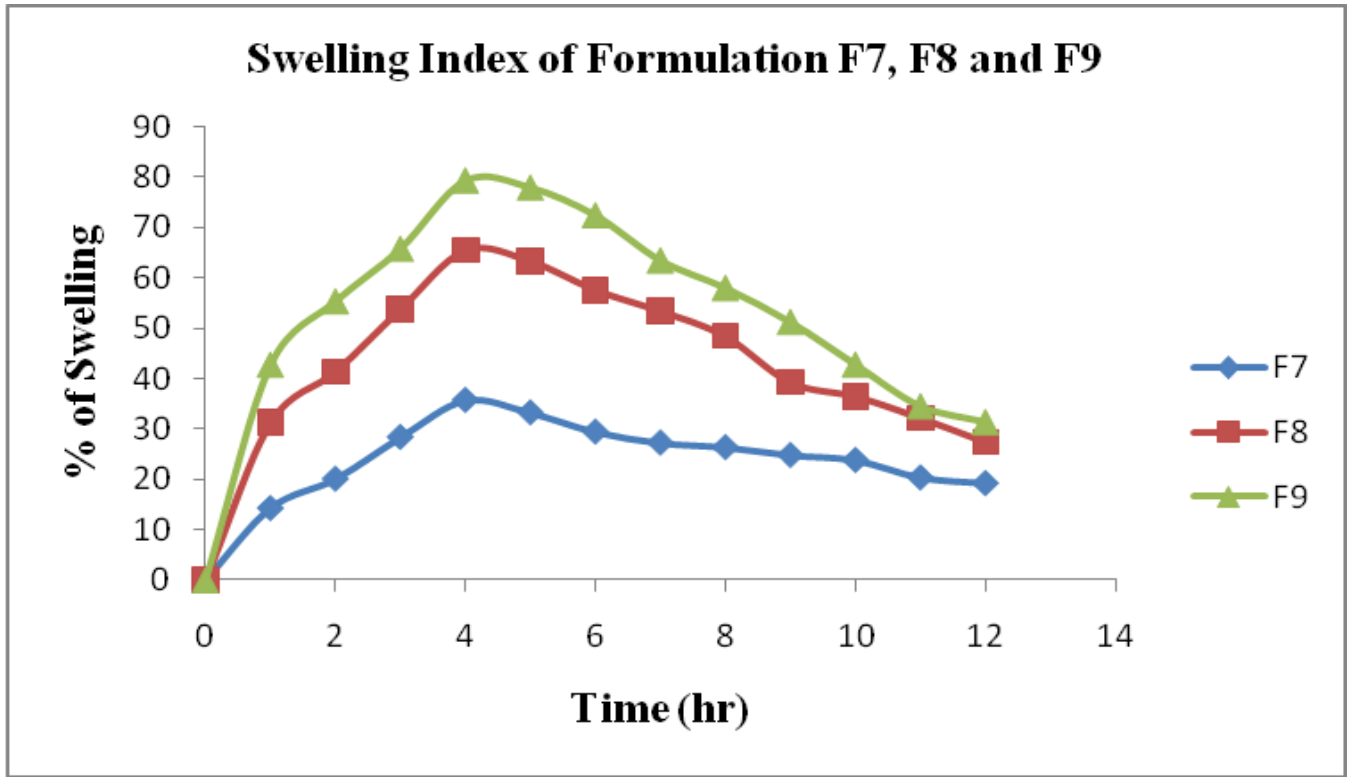

Fig no.17 Swelling Index of Formulations F7,F8 and F9

Table No. 14: *In vitro* drug release profile of Gliclazide from F_1 Formulation: - (HPC K4 M)

Time (hrs)	√T	Log T	Abs*	Conc. (µg/ml)	CDR (mg)	CDR (%)	Log % CDR	Cumulative % drug remained	Cumulative Log % Drug remained
0	0	0	0	0	0	0	0	100	2
1	1	0	0.058	2.636	11.863	19.772	1.296	88.136	1.945
2	1.414	0.301	0.124	5.636	25.363	42.272	1.626	74.636	1.872
3	1.732	0.477	0.18	8.181	36.818	61.363	1.787	63.181	1.800
4	2	0.602	0.243	11.045	49.704	82.840	1.918	50.295	1.701
6	2.449	0.778	0.287	13.045	58.704	97.840	1.990	41.295	1.615

*Each reading is an average of three determinations

Table No. 15: *In vitro* drug release profile of Gliclazide from F_2 Formulation: - HPC 75-100

Time (hrs)	√T	Log T	Abs*	Conc. (µg/ml)	CDR (mg)	CDR (%)	Log % CDR	Cumulative % drug remained	Cumulative Log % Drug remained
0	0	0	0	0	0	0	0	100	2
1	1	0	0.044	2	9	15	1.176	91	1.959
2	1.414	0.301	0.078	3.545	15.954	26.590	1.424	84.045	1.924
3	1.732	0.477	0.125	5.681	25.568	42.613	1.629	74.431	1.871
4	2	0.602	0.179	8.136	36.613	61.022	1.785	63.386	1.801
6	2.449	0.778	0.243	11.045	49.704	82.840	1.918	50.295	1.701
8	2.828	0.903	0.289	13.136	59.113	98.522	1.993	40.886	1.611

*Each reading is an average of three determinations.

Table No. 16: *In vitro* drug release profile of Gliclazide from F_3 Formulation: - HPC 75-100

Time (hrs)	√T	Log T	Abs*	Conc. (µg/ml)	CDR (mg)	CDR (%)	Log % CDR	Cumulative % drug remained	Cumulative Log % Drug remained
0	0	0	0	0	0	0	0	100	2
1	1	0	0.048	2.181	9.818	16.363	1.213	90.181	1.955
2	1.414	0.301	0.084	3.818	17.181	28.636	1.456	82.818	1.918
3	1.732	0.477	0.118	5.363	24.136	40.227	1.604	75.863	1.880
4	2	0.602	0.158	7.181	32.318	53.863	1.731	67.681	1.830
6	2.449	0.778	0.215	9.772	43.977	73.295	1.865	56.022	1.748
8	2.828	0.903	0.251	11.409	51.340	85.568	1.932	48.659	1.687
10	3.162	1	0.288	13.090	58.909	98.181	1.992	41.090	1.613

*Each reading is an average of three determinations

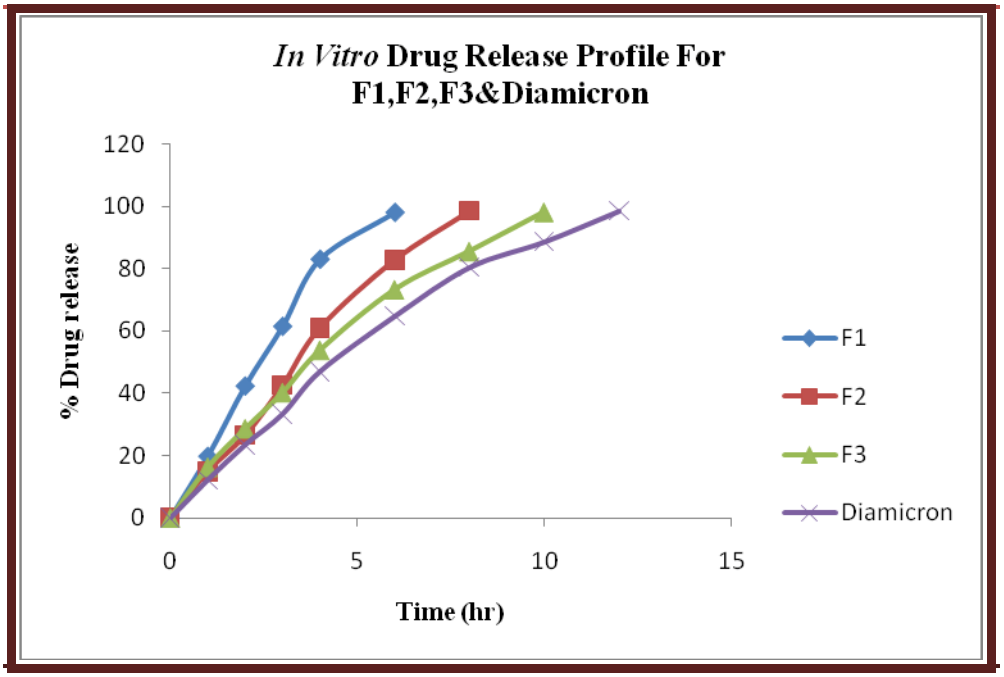

Figure – 18 *In-vitro* drug release profile for F_1, F_2, and F_3formulations

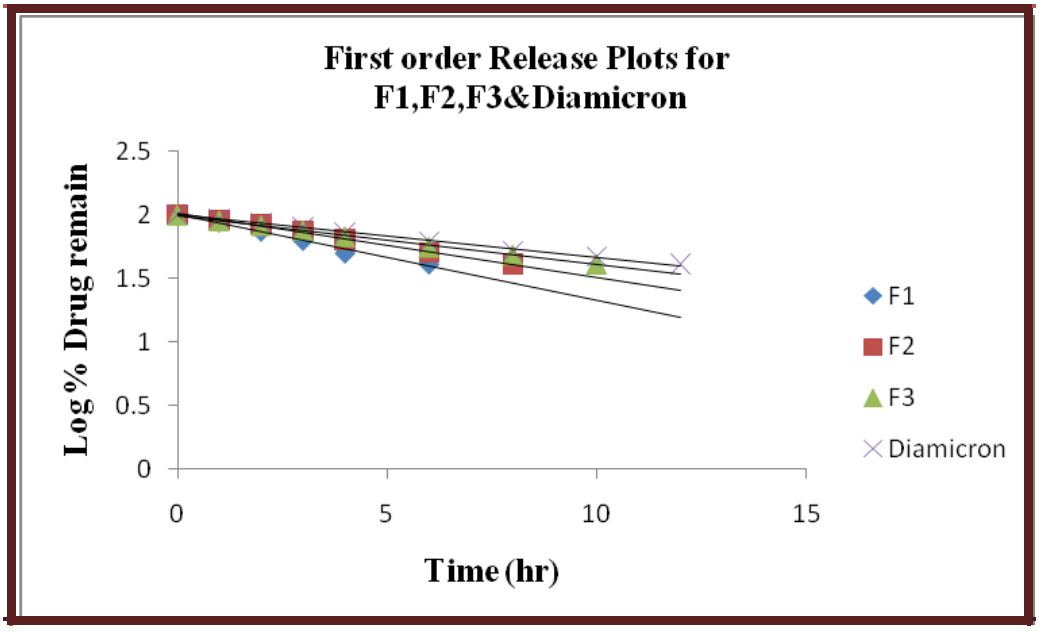

Figure – 19 First order drug release plots F_1, F_2, and F_3 formulations

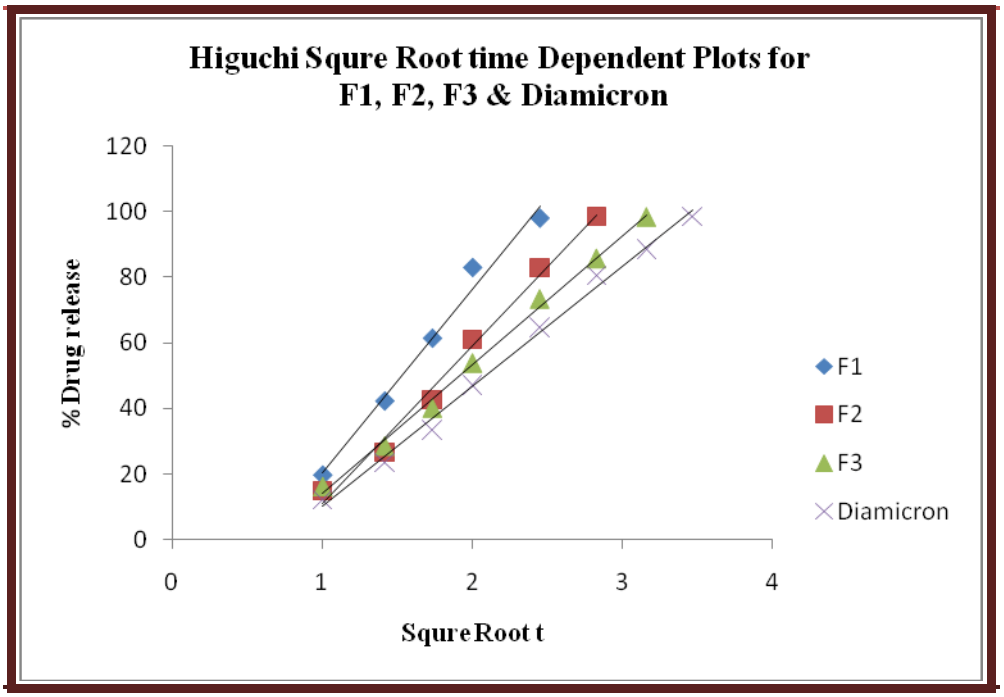

Figure – 20 Higuchi plots for F_1, F_2, and F_3 formulations

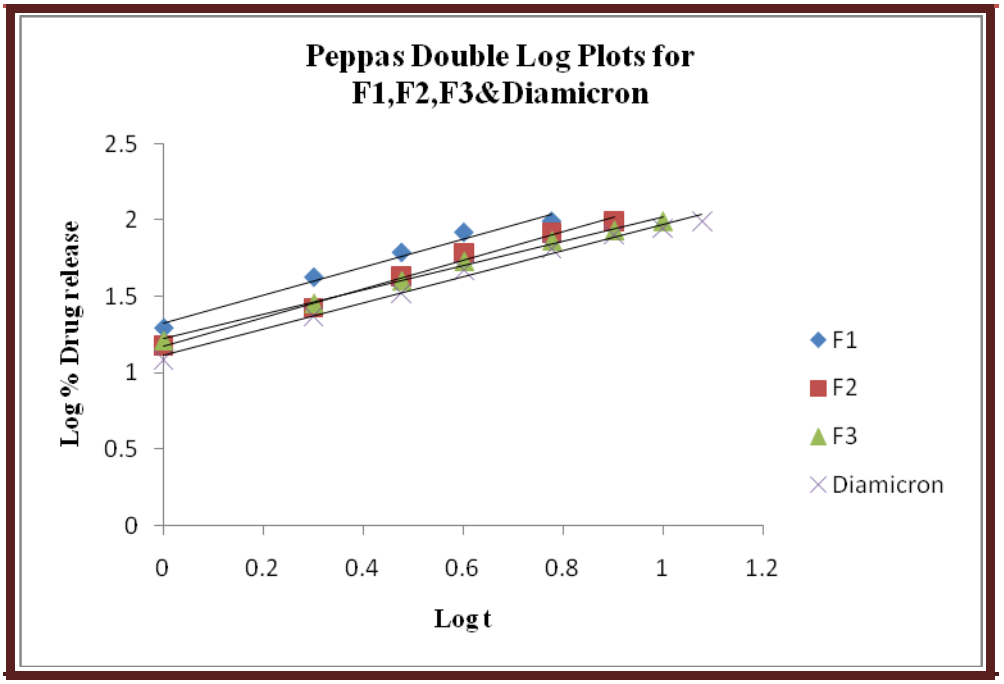

Figure – 21 Peppas double log plots for F_1, F_2, and F_3 formulations

Table No. 17: *In vitro* drug release profile of Gliclazide from F_4 Formulation: - HPMC K-4 M

Time (hrs)	√T	Log T	Abs*	Conc. (µg/ml)	CDR (mg)	CDR (%)	Log % CDR	Cumulative % drug remained	Cumulative Log % Drug remained
0	0	0	0	0	0	0	0	100	2
1	1	0	0.06	2.727	12.272	20.454	1.310	87.727	1.943
2	1.414	0.301	0.131	5.954	26.795	44.659	1.649	73.204	1.864
3	1.732	0.477	0.194	8.818	39.681	66.136	1.820	60.318	1.780
4	2	0.602	0.242	11	49.5	82.5	1.916	50.5	1.703
6	2.449	0.778	0.291	13.227	59.522	99.204	1.996	40.477	1.607

*Each reading is an average of three determinations

Table No. 18: *In vitro* drug release profile of Gliclazide from F_5 Formulation: - HPMC K-4 M

Time (hrs)	√T	Log T	Abs*	Conc. (µg/ml)	CDR (mg)	CDR (%)	Log % CDR	Cumulative % drug remained	Cumulative Log % Drug remained
0	0	0	0	0	0	0	0	100	2
1	1	0	0.054	2.454	11.045	18.409	1.265	88.954	1.949
2	1.414	0.301	0.094	4.272	19.227	32.045	1.505	80.772	1.907
3	1.732	0.477	0.123	5.590	25.159	41.931	1.622	74.840	1.874
4	2	0.602	0.162	7.363	33.136	55.227	1.742	66.863	1.825
6	2.449	0.778	0.201	9.136	41.113	68.522	1.835	58.886	1.770
8	2.828	0.903	0.243	11.045	49.704	82.840	1.918	50.295	1.701
10	3.162	1	0.287	13.045	58.704	97.840	1.990	41.295	1.615

*Each reading is an average of three determinations

Table No. 19: *In vitro* drug release profile of Gliclazide from F_6 Formulation: - HPMC K-4 M

Time (hrs)	√T	Log T	Abs*	Conc. (µg/ml)	CDR (mg)	CDR (%)	Log % CDR	Cumulative % drug remained	Cumulative Log % Drug remained
0	0	0	0	0	0	0	0	100	2
1	1	0	0.037	1.681	7.568	12.613	1.100	92.431	1.965
2	1.414	0.301	0.069	3.136	14.113	23.522	1.371	85.886	1.933
3	1.732	0.477	0.097	4.409	19.840	33.068	1.519	80.159	1.903
4	2	0.602	0.133	6.045	27.204	45.340	1.656	72.795	1.862
6	2.449	0.778	0.179	8.136	36.613	61.022	1.785	63.38	1.801
8	2.828	0.903	0.236	10.727	48.272	80.454	1.905	51.727	1.713
10	3.162	1	0.259	11.772	52.977	88.295	1.945	47.022	1.672
12	3.464	1.079	0.288	13.090	58.909	98.181	1.992	41.090	1.613

*Each reading is an average of three determinations

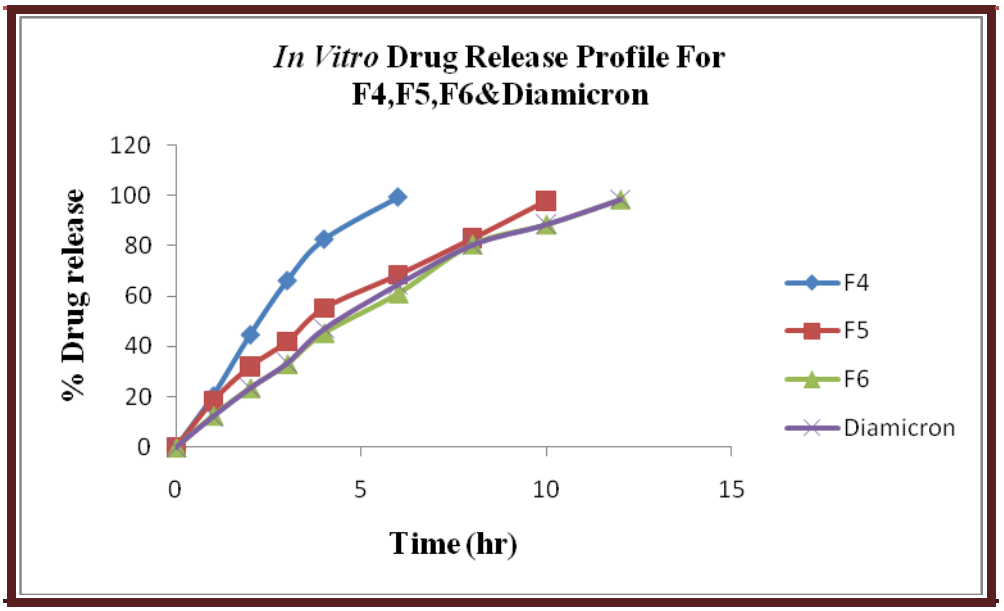

Figure – 22 *In-vitro* drug release profile for F_4, F_5, and F_6 formulations

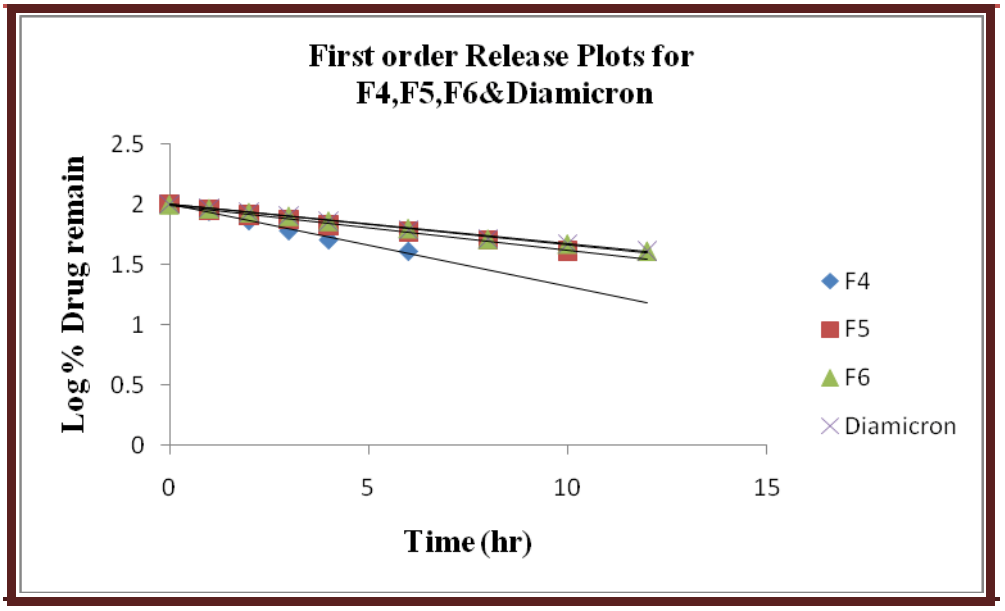

Figure – 23 First order drug release plots for F_4, F_5, and F_6 formulations

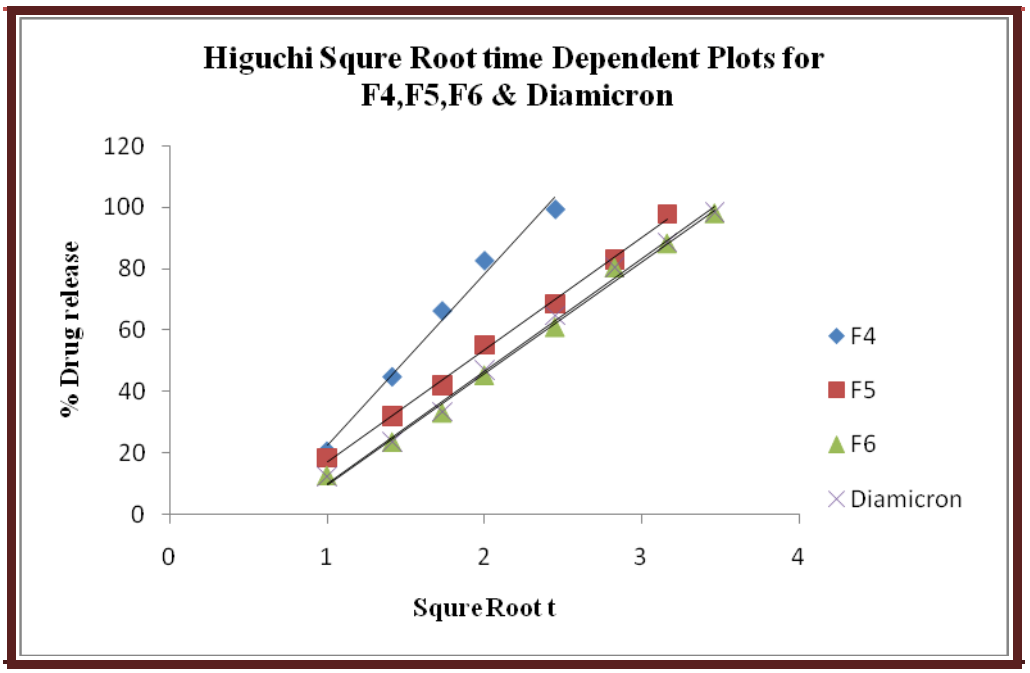

Figure – 24 Higuchi plots for F_4, F_5, and F_6 formulations

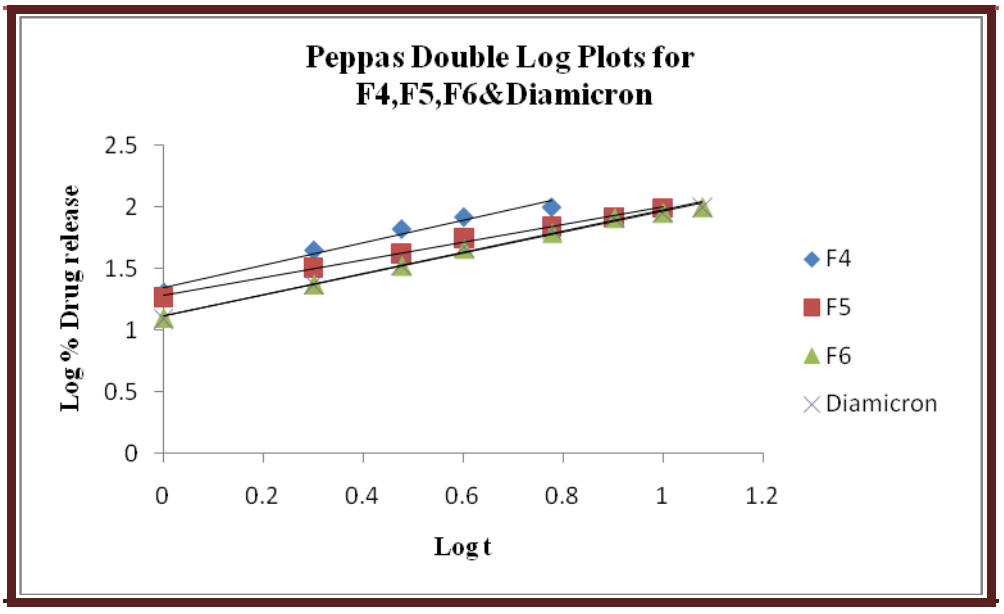

Figure – 25 Peppas double log plots for F_4, F_5, and F_6 formulations

Table No. 20: *In vitro* drug release profile of Gliclazide from F_7 Formulation: - HPMC K-4 M + HPC 75-100

Time (hrs)	√T	Log T	Abs*	Conc. (µg/ml)	CDR (mg)	CDR (%)	Log % CDR	Cumulative % drug remained	Cumulative Log % Drug remained
0	0	0	0	0	0	0	0	100	2
1	1	0	0.049	2.227	10.022	16.704	1.222	89.977	1.954
2	1.414	0.301	0.093	4.227	19.022	31.704	1.501	80.977	1.908
3	1.7320	0.477	0.141	6.409	28.840	48.068	1.681	71.159	1.852
4	2	0.602	0.182	8.272	37.227	62.045	1.792	62.772	1.797
6	2.449	0.778	0.246	11.181	50.318	83.863	1.923	49.681	1.696
8	2.828	0.903	0.288	13.090	58.909	98.181	1.992	41.090	1.613

*Each reading is an average of three determinations

Table No. 21: *In vitro* drug release profile of Gliclazide from F_8 Formulation: - HPMC K-4 M + HPC 75-100

Time (hrs)	√T	Log T	Abs*	Conc. (µg/ml)	CDR (mg)	CDR (%)	Log % CDR	Cumulative % drug remained	Cumulative Log % Drug remained
0	0	0	0	0	0	0	0	100	2
1	1	0	0.044	2	9	15	1.176	91	1.959
2	1.414	0.301	0.084	3.818	17.181	28.636	1.456	82.818	1.918
3	1.732	0.477	0.112	5.090	22.909	38.181	1.581	77.090	1.887
4	2	0.602	0.144	6.545	29.454	49.090	1.691	70.545	1.848
6	2.449	0.778	0.189	8.590	38.659	64.431	1.809	61.340	1.787
8	2.828	0.903	0.245	11.136	50.113	83.522	1.921	49.886	1.697
10	3.162	1	0.287	13.045	58.704	97.840	1.990	41.295	1.615

*Each reading is an average of three determinations

Table No. 22: *In vitro* drug release profile of Gliclazide from F_9 Formulation: - HPMC K-4 M + HPC 75-100

Time (hrs)	√T	Log T	Abs*	Conc. (µg/ml)	CDR (mg)	CDR (%)	Log % CDR	Cumulative % drug remained	Cumulative Log % Drug remained
0	0	0	0	0	0	0	0	100	2
1	1	0	0.036	1.636	7.363	12.272	1.088	92.636	1.966
2	1.414	0.301	0.066	3	13.5	22.5	1.352	86.5	1.937
3	1.732	0.477	0.092	4.181	18.818	31.363	1.496	81.181	1.909
4	2	0.602	0.138	6.272	28.227	47.045	1.672	71.772	1.855
6	2.449	0.778	0.183	8.318	37.431	62.386	1.795	62.568	1.796
8	2.828	0.903	0.235	10.681	48.068	80.113	1.903	51.931	1.715
10	3.162	1	0.264	12	54	90	1.954	46	1.662
12	3.464	1.079	0.291	13.227	59.522	99.204	1.996	40.477	1.607

*Each reading is an average of three determinations

Table No. 23: *In vitro* drug release profile of Gliclazide from Diamicron Formulation: -

Time (hrs)	√T	Log T	Abs*	Conc. (µg/ml)	CDR (mg)	CDR (%)	Log % CDR	Cumulative % drug remained	Cumulative Log % Drug remained
0	0	0	0	0	0	0	0	100	2
1	1	0	0.036	1.636	7.363	12.272	1.088	92.636	1.966
2	1.414	0.301	0.069	3.136	14.113	23.522	1.371	85.886	1.933
3	1.732	0.477	0.098	4.454	20.045	33.409	1.523	79.954	1.902
4	2	0.602	0.138	6.272	28.227	47.045	1.672	71.772	1.855
6	2.449	0.778	0.19	8.636	38.863	64.772	1.811	61.136	1.786
8	2.828	0.903	0.236	10.727	48.272	80.454	1.905	51.727	1.713
10	3.162	1	0.26	11.818	53.181	88.636	1.947	46.818	1.670
12	3.464	1.079	0.289	13.136	59.113	98.522	1.993	40.886	1.611

*Each reading is an average of three determinations.

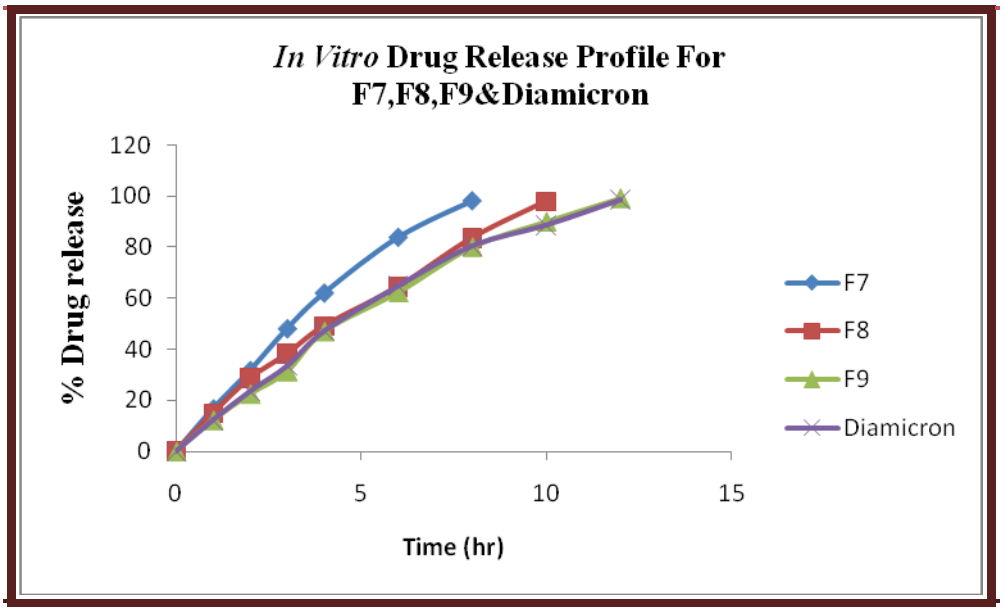

Figure – 26 *In-vitro* drug release profile for F_7, F_8, and F_9 formulations

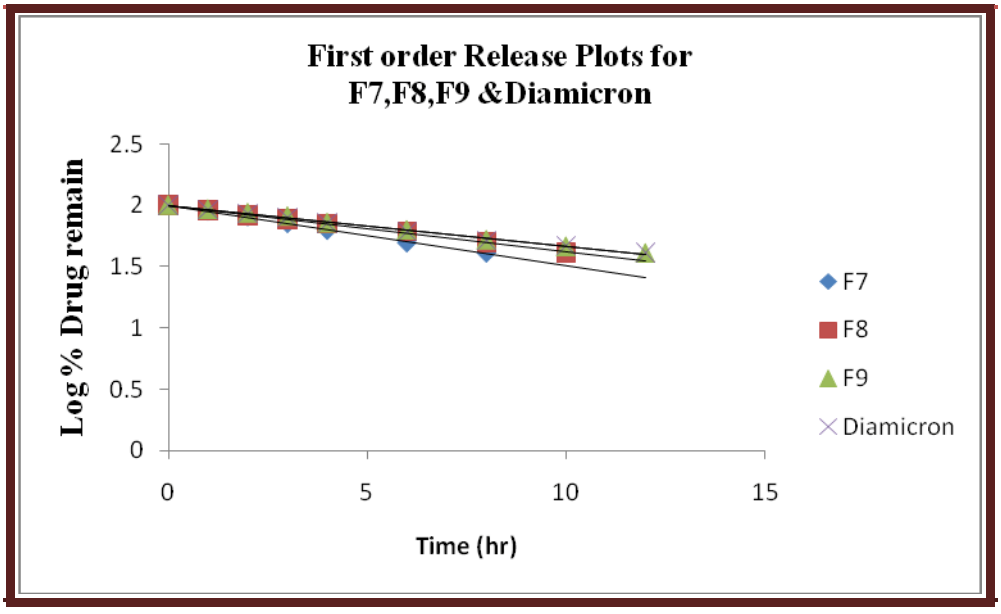

Figure – 27 First order drug release plots for F_7, F_8, and F_9 formulations

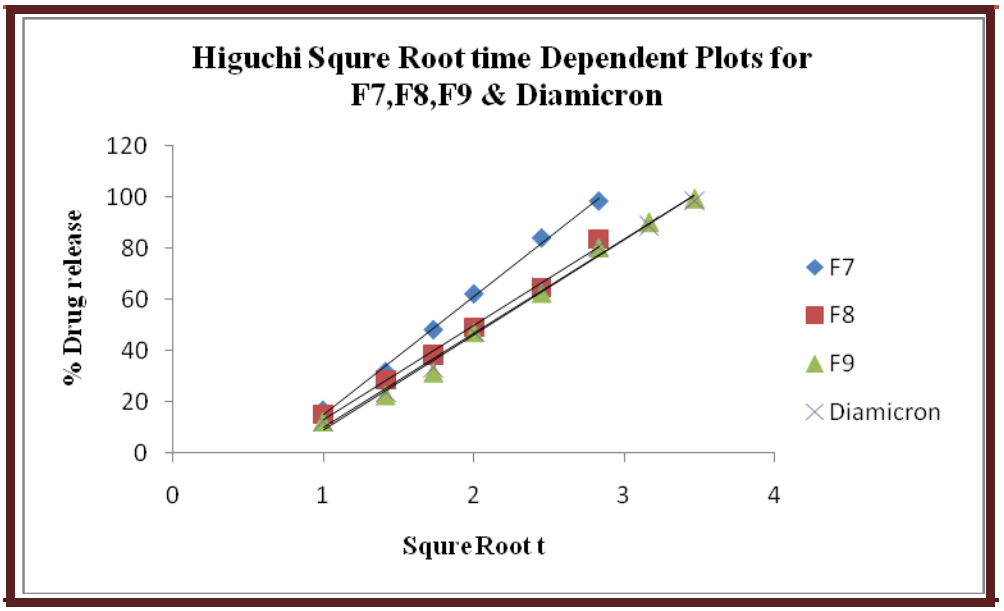

Figure – 28 Higuchi plots for F_7, F_8, and F_9 formulations

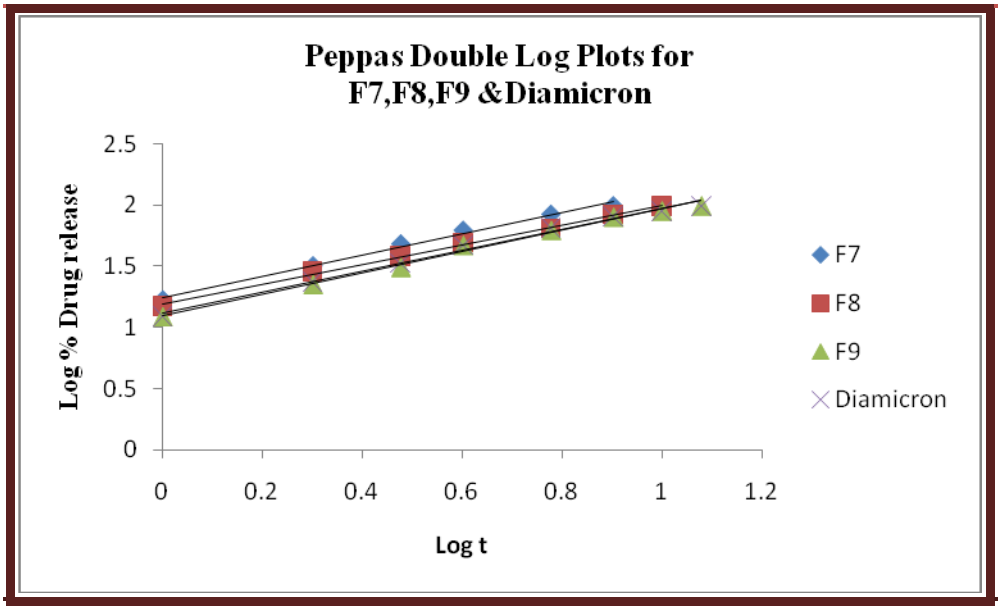

Figure – 29 Peppas double log plots for F_7, F_8, and F_9 formulations

Table No. 24: *In vitro* drug release for all tablets formulation

TIME (Hrs)	FORMULATIONS									
	F1	**F2**	**F3**	**F4**	**F5**	**F6**	**F7**	**F8**	**F9**	**Diamicron**
0	0	0	0	0	0	0	0	0	0	0
1	19.772	15	16.363	20.454	18.409	12.613	16.704	15	12.272	12.272
2	42.272	26.590	28.636	44.659	32.045	23.522	31.704	28.636	22.5	23.522
3	61.363	42.613	40.227	66.136	41.931	33.068	48.068	38.181	31.363	33.409
4	82.840	61.022	53.863	82.5	55.227	45.340	62.045	49.090	47.045	47.045
6	97.840	82.840	73.295	99.204	68.522	61.022	83.863	64.431	62.386	64.772
8		98.522	85.568		82.840	80.454	98.181	83.522	80.113	80.454
10			98.181		97.840	88.295		97.840	90	88.636
12						98.181			99.204	98.522

Table No. 25: Curve fitting data for all tablet formulations

FORMULATION	ZERO ORDER		FIRST ORDER			HIGUCHI		PEPPAS	
	Slope (K)	R^2	Slope	(K)	R^2	Slope (K)	R^2	Slope (n)	R^2
F1	16.96	0.964	-0.067	-0.1543	0.987	55.965	0.985	0.919	0.980
F2	12.69	0.985	-0.050	-0.1152	0.995	48.145	0.989	0.943	0.991
F3	9.734	0.973	-0.039	-0.0898	0.997	39.075	0.996	0.794	0.995
F4	17.09	0.958	-0.068	-0.1566	0.989	55.755	0.988	0.902	0.974
F5	9.298	0.969	-0.037	-0.0852	0.995	36.479	0.997	0.717	0.996
F6	8.276	0.976	-0.033	-0.076	0.995	36.379	0.994	0.841	0.995
F7	12.43	0.978	-0.049	-0.1128	0.998	46.079	0.997	0.869	0.993
F8	9.536	0.987	-0.037	-0.0852	0.997	38.372	0.994	0.804	0.998
F9	8.433	0.976	-0.033	-0.076	0.996	37.25	0.993	0.865	0.992
Diamicron	8.320	0.971	-0.033	-0.076	0.995	36.617	0.995	0.852	0.991

Table No .26: Assay and Releated substances in the F6, F9 & Diamicron Formulations

Formulations	Assay	Related Substances
F6	98.90%	0.53%
F9	98.67%	0.44%
Diamicron	99.01%	0.58%

*Each reading is an average of three determinations.

Table No 27: Stability data of F6 formulation

Time in months	Formulation F6 stored at 40^0C/ 75% RH	
	Physical appearance	% Drug content
1	+++	98.76
2	+++	98.38
3	++	97.98

+++ = Same as on zero day, ++ = Slight change in color

Table No 28: Stability data of F9 formulation

Time in months	Formulation F9 stored at 40^0C/ 75% RH	
	Physical appearance	% Drug content
1	+++	98.45
2	+++	99.76
3	++	98.89

+++ = Same as on zero day, ++ = Slight change in color

VI) *In-vitro* Dissolution Study.

The *in-vitro* drug release of the entire matrix tablets were carried in phosphate buffer pH 7.4 from 0 to 12 hrs by USP XXIV type-II apparatus and the values are shown in Table no. 10 to 18. The plot of % Cumulative drug release v/s time (hrs) was plotted and depicted as shown in Fig no18 and 22.

From the *in-vitro* dissolution data, it was found that the drug release from marketed sample Diamicron XR containing gliclazide is 98.52% in 12 hrs, Hydroxy propyl cellulose 24% (F1) 97.84 % in 6 hrs, Hydroxy propyl cellulose 28% (F2) 98.52% in 08 hrs, Hydroxy propyl cellulose 32% (F3) 98.18% in 10 hrs. Hydroxy propyl methyl cellulose 24% (F_4) 99.20% in 06 hrs, Hydroxy propyl methyl cellulose 28% (F_5) 97.84% in 10 hrs, Hydroxy propyl methyl cellulose 32% (F6) 98.18% in 12 hrs, where as in case of Hydroxy propyl methyl cellulose and Hydroxy propyl cellulose combination 24 % (F7) 98.18% in 08 hrs, Hydroxy propyl methyl cellulose and Hydroxy propyl cellulose combination 28% (F8) 97.84% in 10 hrs and Hydroxy propyl methyl cellulose and Hydroxy propyl cellulose combination 32% (F9) 99.20% in 12 hrs.

From the results it was observed that increasing the amount of polymer in the formulations, resulted in slower rate and decreased amount of drug release from the tablet. Comparison between Hydroxy propyl cellulose, Hydroxy propyl methyl cellulose and combination of Hydroxy propyl cellulose and Hydroxy propyl methyl cellulose based tablets, release of drug from Hydroxy propyl cellulose based tablet was found to be more faster compared to Hydroxy propyl cellulose and Hydroxy propyl methyl cellulose based tablet. The maximum drug release was found to be 98.18% over a period of 12 hours in Hydroxy propyl methyl cellulose based tablets

(F_6). Similarly maximum drug release was found to be 99.20% over a period of 12hours in Hydroxy propyl cellulose and Hydroxy propyl methyl cellulose based tablets (F_9). This indicates that the minimum quantity of Hydroxy propyl cellulose and maximum quantity of Hydroxy propyl methyl cellulose required to prepare the sustain

release matrix tablets of Gliclazide.

Order of retardation of different formulation is in the following sequence

Hydroxy propyl methyl cellulose **>** Hydroxy propyl cellulose .

VII) Curve Fitting Analysis.

Table no.20 shows data analysis of release profiles according to different kinetics models. The kinetic treatment reflected that release data of Hydroxy propyl cellulose formulation that is F1, F2 & F3 showed higher r^2 values for first order plot indicating that release of drug follows first order kinetic, further Korsmeyer and peppas equation resulted into the value of n in the range of 0.980 to 0.995 with all the tablets indicating a non-fickian diffusion mechanism and may indicate that the drug release is controlled by more than one process.

The kinetic treatment reflected that release data of Hydroxy propyl methyl cellulose formulation that is F4, F5 & F6 showed higher r^2 values for First order plot indicating that release of drug follows first order kinetic, further Korsmeyer and peppas equation resulted into the value of n in the range of 0.974 to 0.996 with all the tablets indicating a non-fickian diffusion mechanism and may indicate that the drug release is controlled by more than one process.

The kinetic treatment reflected that release data of Hydroxy propyl methyl cellulose and Hydroxy propyl cellulose combination formulation that is F7, F8 & F9 showed

higher r^2 values for first order plot indicating that release of drug follows first order kinetic, further Korsmeyer and peppas equation resulted into the value of n of n in the range of 0.992 to 0.998 with all the tablets indicating a non-fickian diffusion mechanism and may indicate that the drug release is controlled by more than one process.

IX) Stability Studies.

The selected Formulation F6 & F9 were evaluated for stability studies which were stored at 40^0C at 75% RH tested for 3 months and were analyzed for their drug content at the monthly interval. The residual drug contents of formulations were found to be within the permissible limits and the results of 3 months duration are shown in the Table no 21 & 22 which was estimated by seeing drug content uniformity.

In present investigation an attempt has been made to design and develop some Gliclazide matrix tablets using Hydroxy propyl cellulose, Hydroxy propyl methyl cellulose and their combination as release retarding polymers. Gliclazide is oral hypoglycaemic drug which lowers blood glucose level and has been selected to prepare sustained release dosage forms.

1. Gliclazide sustained release matrix tablet were prepared using Hydorxy Propyl Cellulose, Hydroxy Propyl Methyl Cellulose and their combination as base polymer by wet granulation method.
2. FT-IR spectral analysis showed that characteristic peak of Gliclazide pure drug was retained in the spectra of all the formulations indicating the inactness of the drug in all the formulations.

3. The prepared tablets were evaluated for number of parameters like thickness, diameter, weight variation, swelling index and *in vitro* release studies.
4. All the prepared tablets were of smooth surface and elegant texture.
5. The tablets prepared were checked visually for its appearance & surface texture.
6. The weights of the tablets were in the range of 250 ± 5 mg. The thickness of the tablet was in the range of 4.45 ± 0.11 to 4.51 ± 0.12 mm.

   As the time increases, the swelling index was increased; later on it decreases gradually due to dissolution of outermost –gelled layer of tablet into dissolution medium. Comparison between Hydroxy Propyl Cellulose and Hydroxy Propyl Methyl Cellulose, It has been observed that swelling index is more in Hydroxy Propyl Methyl Cellulose. Drug content uniformity study showed uniform dispersion of the drug throughout the formulation in the range of 97.00 ±0.24 to 99.72 ±0.30 %.
7. The maximum drug release was found to be 98.18% over a period of 12 hours in HPMC K4M based tablets (F_6). Similarly maximum drug release was found to be 99.20% over a period of 12 hours in HPC 75-100 & HPMC K4M based tablets (F_9) and maximum drug release was found to be 98.52% over a period of 12 hours in marketed formulation Diamicron. This indicates that the minimum quantity of HPC 75-100 and maximum quantity of HPMC required to prepare the sustain release matrix tablets of Gliclazide.

8. The formulations were also subjected to model fitting analysis to know the order and mechanism of drug release from the formulations by treating the data according to zero – order, *first – order*, *Higuchi* and peppas equations. The data clearly shows that, the release kinetics revealed that the formulations containing HPMC K4M follows *first – order* drug release with non-fickian diffusion, formulation containing HPC 75-100 & HPMC K4M follows *first – order* drug release with non-fickian diffusion and the marketed sample Diamicron follows *first – order* drug release with non-fickian diffusion.
9. Stability studies reveled that there were no significant changes in physical properties and drug contain of formulation F6 & F9 thus formulation were stable.
10. It can be concluded that Hydroxy Propyl Cellulose and Hydroxy Propyl Methyl Cellulose combination and individual Hydroxy Propyl Methyl Cellulose respectively can be used as an effective matrix former to sustain the release of Gliclazide for an extended period of 12 hrs.

In present investigation an attempt has been made to design and develop some Gliclazide matrix tablets using Hydroxy propyl cellulose, Hydroxy propyl methyl cellulose and their combination as release retarding polymers.

Gliclazide is oral hypoglycaemic drug which lowers blood glucose level and has been selected to prepare sustained release dosage forms.

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